Advisory Committee Briefing Document for Meridia® (sibutramine hydrochloride monohydrate)

Endocrinologic and Metabolic Drugs Advisory Committee

Meeting on 15 September 2010

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Abbreviations

ACE	angiotensin-converting enzyme
ARB	angiotensin II receptor blocker
BfArM	German Federal Institute for Drugs and Medical Devices
BL	baseline
BMI	body mass index
bpm	beats per minute
CABG	coronary artery bypass graft
CAD	coronary artery disease
CCDS	company core data sheet
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CNS	central nervous system
CPMP	European Committee for Proprietary Medicinal Products
CT	computed tomography
CV	cardiovascular
CVA	cerebrovascular accident
DBP	diastolic blood pressure
DEA	Drug Enforcement Agency
DHCP	dear health care provider
DIFF	point estimate of the difference between sibutramine and placebo groups
DM	diabetes mellitus
DSMB	data safety monitoring board
E/100PY	events per 100 person-years
EAC	events adjudication committee
EMA	European Medicines Agency
ESC	executive steering committee
EU	European Union
FDA	Food and Drug Administration
HbA_{1c}	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol

HR	hazard ratio
ICT	integrated clinical trials
ITT	intent-to-treat
KM	Kaplan-Meier
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
M	month
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MMRM	mixed-effects model repeated measures
MRI	magnetic resonance imaging
MRP	mutual recognition procedure
NDA	new drug application
NMS	neuroleptic malignant syndrome
NYHA	New York Heart Association
PAOD	peripheral arterial occlusive disease
PBO	placebo
PCOS	polycystic ovary syndrome
POE	primary outcome events
PTCA	percutaneous transluminal coronary angioplasty
PTY	patient treatment-year
PY	person-year
RCA	resuscitated cardiac arrest
REMS	risk evaluation and mitigation strategy
RMS	reference member state
SAWP	Scientific Advice Working Party
SBP	systolic blood pressure
SBT	sibutramine
SD	standard deviation
SmPC	summary of product characteristics
SMQ	standardized MedDRA query
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TC	total cholesterol

TG	triglycerides
TIA	transient ischemic attack
TZD	thiazolidinedione
US	United States
VLDL-C	very low-density lipoprotein cholesterol
WBC	white blood cell
WHO	World Health Organization
Wk	Week

Definitions

ITT population, also referred to as the All Subjects population	In SCOUT, the ITT population consisted of all randomized subjects dispensed randomized study drug. Subjects were grouped according to the treatment they were randomized to receive for all analyses of the ITT population.
Lead-in Period Safety population	In SCOUT, the Lead-in Period Safety population consisted of all subjects who took at least one dose of sibutramine during the Lead-in Period and only included data from the Lead-in Period.
Randomization Phase Safety population	In SCOUT, the Randomization Phase Safety population consisted of all subjects who took at least one dose of study drug during the Treatment Period. Subjects were grouped according to the treatment they actually received at the beginning of the Treatment Period.
Weight Loss Responders	Weight Loss Responders were defined as subjects who lost at least 5% of their baseline weight at Month 1 and/or Month 2 of the double-blind Treatment Period.
Vital Signs Outliers	Vital Signs Outliers were defined as subjects with increases above lead-in baseline in systolic or diastolic blood pressure (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment.
Weight Loss/ Vital Signs Conformers	Weight Loss/Vital Signs Conformers were defined as subjects who were Weight Loss Responders and who did not meet criteria for vital signs outliers (i.e., were Vital Signs Non-Outliers).

2.0 Executive Summary

Sibutramine is a centrally-acting weight loss agent that has been marketed globally for over 10 years. Multiple clinical trials have consistently shown that sibutramine promotes weight loss to an extent considered clinically relevant, consistent with the 2007 Draft FDA Guidance for Industry "Developing Products for Weight Management."[1] Compared to placebo, sibutramine treatment results in:

- Greater mean absolute and percentage weight loss (4.08 kg and 4.28% difference from placebo at 12 months)
- Greater percentage of subjects achieving ≥ 5%, ≥ 10%, and ≥ 15% weight loss (26.5%, 14.7%, and 7.6%, difference from placebo at 12 months)

In general, 3 months of treatment with sibutramine is adequate to identify those who respond to treatment (i.e., achieve at least 5% weight loss). Continued use of sibutramine in weight loss responders results in maintenance of achieved weight loss. Sibutramine use is also associated with improvements in obesity-related risk factors (triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]) to an extent that is commensurate with the degree of weight loss achieved.

The safety profile of sibutramine is well characterized, based on extensive clinical trial experience and worldwide postmarketing exposure estimated at greater than 6 million patient treatment-years. The most commonly observed adverse events with sibutramine are dry mouth, anorexia, insomnia, constipation, headache, and rhinitis. Although sibutramine is a centrally-acting agent, it has not been associated with significant central nervous system (CNS) events.

Sibutramine's effect of increasing blood pressure and pulse in some patients is well known. As described in the US label for Meridia®, sibutramine has been associated with mean increases as compared to placebo in systolic and diastolic blood pressure of 1 to 3 mmHg and in pulse of 4 to 5 beats per minute (bpm). Routine monitoring of blood pressure and pulse is recommended in the US label. Importantly, most patients who

experience sustained increases in blood pressure and pulse on sibutramine can be identified early (within the initial 3 months) and discontinued from treatment. Additionally, the use of sibutramine is contraindicated in patients with a history of cardiovascular disease.

As a postapproval commitment, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) required the conduct of the Sibutramine Cardiovascular OUTcomes (SCOUT) study, a cardiovascular (CV) outcomes study to evaluate the long-term consequences of sibutramine's effect on blood pressure and pulse. SCOUT was a randomized, double-blind, placebo-controlled, parallel-group study with a 6-week lead-in period, during which all subjects were treated with sibutramine.

Due to concern that the CV outcome event rate in an obese "on-label" population would be so low as to make an outcomes study impractical (i.e., such a study would take too long or would require an exceedingly large number of subjects), the CHMP required a number of design features to ensure that an adequate CV outcome event rate would be observed in SCOUT. These design features included the enrollment of a largely contraindicated, high-CV-risk population to be treated for an extended duration of time (up to 6 years), regardless of weight loss.

The primary endpoint analysis for SCOUT was the time-to-event analysis of the composite of primary outcome events (POE; composite of nonfatal myocardial infarction [MI], nonfatal stroke, resuscitated cardiac arrest, and CV death). The primary endpoint result for the intent-to-treat (ITT) population (also referred to herein as the All Subjects population) showed a 16% increased risk for POE in the sibutramine group (sibutramine 11.4%, placebo 10.0%; hazard ratio [HR] = 1.162, 95% CI = 1.029–1.311), which was due primarily to an increased risk for nonfatal MI and nonfatal stroke events. No increased risk of death (CV Death [HR = 0.984, 95% CI = 0.831–1.166] or All-Cause Mortality [HR = 1.043, 95% CI = 0.910–1.196]) was observed.

While the results of SCOUT can be readily applied to subjects who were enrolled in the study and managed according to the protocol, a significant challenge exists in understanding how the results apply to the use of sibutramine in the indicated "on-label" population and when used as directed. Specifically, sibutramine is not indicated for use in patients with a history of cardiovascular disease and therapy would not be continued for an extended period of time in patients who do not achieve weight loss. The extrapolation of the results of SCOUT to the on-label population required assessment of not only the prespecified analyses but also of post hoc analyses, which include covariates affected by treatment. Importantly, when these additional analyses are taken into account, the results of SCOUT can be used to inform the appropriate use of sibutramine.

Analyses from SCOUT show that the risk of POE was not increased in the sibutramine-treated subjects who would have met criteria for appropriate use consistent with clinical practice and product labeling. Findings from these important analyses are summarized below:

- Sibutramine is contraindicated in patients with a history of cardiovascular disease. *However, such patients were included in SCOUT.*
  - SCOUT subjects were categorized into 1 of 3 protocol-specified CV risk groups: 1) those with a history of Type 2 diabetes mellitus (DM) with an additional risk factor (DM Only group), 2) those with a history of cardiovascular disease (CV Only group), 3) and those meeting both criteria (CV + DM group).
  - Results based on the prespecified CV risk groups showed that the increased risk for nonfatal events with sibutramine was observed in the groups with a known medical history of cardiovascular disease (CV Only and CV + DM groups); however, no increased risk for POE was seen in the group without a history of known cardiovascular disease (that is, the DM Only group) (sibutramine 6.0%, placebo 6.1%; HR = 1.002, 95% CI = 0.718–1.398).
- Sibutramine use should be discontinued in patients with sustained increases in blood pressure or pulse. *However, SCOUT included some subjects with sustained increases in blood pressure and pulse.*

- In post hoc analyses, subjects with increases in blood pressure (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment were classified as "Vital Signs Outliers." "Vital Signs Non-Outliers" did not meet this criterion.
- Sibutramine Vital Signs Non-Outliers (10.7%) had a lower risk for POE as compared to the sibutramine Vital Signs Outliers (12.7%) in the All Subjects population (HR = 0.864, 95% CI = 0.729–1.024).
- No difference in risk for POE was seen between sibutramine (10.7%) and placebo Vital Signs Non-Outliers (10.4%) in the All Subjects population (HR = 1.047, 95% CI = 0.904–1.214).

- Sibutramine use should be discontinued in patients who do not achieve adequate weight loss response. *However, subjects in SCOUT continued in the study regardless of weight loss.*
  - Subjects with at least 5% weight loss during the first 3 months of treatment were classified as "Weight Loss Responders." "Weight Loss Nonresponders" did not meet this criterion.
  - Sibutramine Weight Loss Responders (9.5%) had a lower risk of POE as compared to sibutramine Weight Loss Nonresponders (12.3%) in the All Subjects data set (HR = 0.808, 95% CI = 0.668–0.979).
- Even in the high-CV-risk SCOUT All Subjects population, sibutramine-treated subjects showed no increased risk of POE if they met both the Vital Signs Non-Outlier and Weight Loss Responder criteria.
  - Subjects with both Weight Loss Response and Vital Signs Non-Outlier status were classified as "Weight Loss/Vital Signs Conformers." "Weight Loss/Vital Signs Nonconformers" did not meet these criteria.
  - Sibutramine Weight Loss/Vital Signs Conformers (8.1%) had a lower risk of POE as compared to sibutramine Weight Loss/Vital Signs Nonconformers (12.3%) in the All Subjects data set (HR = 0.673, 95% CI = 0.532–0.853).
  - No difference in risk for POE was seen between sibutramine (8.1%) and placebo Weight Loss/Vital Signs Conformers (7.9%) in the All Subjects data set (HR = 1.019, 95% CI = 0.727–1.428).

- Furthermore, although the numbers are small, in the DM Only group, the sibutramine Weight Loss/Vital Signs Conformers (3.9%) had a suggestion of a lower risk of POE than placebo Weight Loss/Vital Signs Conformers (5.5%) (HR = 0.773, 95% CI = 0.304–1.966).

SCOUT, therefore, shows no increased risk of CV outcome events for sibutramine-treated subjects who lost weight and had no sustained increases in blood pressure or pulse. These data are consistent with a review of sibutramine clinical trials and worldwide postmarketing safety data, which show that the use of sibutramine in the target population is associated with a low absolute rate of CV outcome events.

Furthermore, the results of SCOUT do not exclude the possibility that a benefit based on CV outcome events might be observed in patients with no history of cardiovascular disease treated for an extended period under appropriate conditions of use.

On the basis of the registration program and a review of sibutramine clinical trials, a 3-month course of sibutramine, to determine who should continue long-term treatment, has a minimal risk of cardiovascular events in the indicated population. Moreover, even in the high-CV-risk population enrolled in SCOUT, 3 months of exposure to sibutramine was associated with a low rate of outcome events.

In summary, SCOUT does not fundamentally alter the established positive benefit-risk profile of sibutramine when used as indicated. The findings from SCOUT validate the appropriateness of the current US label for Meridia, which contraindicates the use of sibutramine in patients with a known history of cardiovascular disease. On the basis of the findings from SCOUT, however, current guidance in the US label regarding the need to monitor blood pressure, pulse, and weight loss, and advice on when to adjust or discontinue Meridia therapy should be revised. Abbott proposes to provide additional advice on monitoring and discontinuation of therapy based on blood pressure, pulse, and weight loss parameters as a boxed warning in the US label for Meridia. Abbott is also proposing a number of risk mitigation strategies to better ensure appropriate use of sibutramine.

3.0 Obesity and Benefits of Weight Loss

Obesity is recognized as a serious medical condition of epidemic proportions and is associated with significant morbidity and mortality.[2] Obesity is commonly defined as a body mass index (BMI) of 30 kg/m^2 or greater. Adults with a BMI in the range of 25 to 29.9 kg/m^2 are classified as overweight. According to the most current estimates (based on 2005 statistics), there are approximately 1.6 billion overweight adults, of whom 400 million are obese.[3] The World Health Organization (WHO) projects that, by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese.

Attempts to meet the Healthy People 2010 initiative and reduce the prevalence of overweight adults in the US to 15% have failed.[4] Approximately 33.8% of US adults are obese and estimates for overweight and obesity combined are 68.0%.[5] Efforts to manage weight through diet and exercise, the cornerstone of weight loss treatment,[6] are often disappointing, particularly outside the clinical trials setting.[7]

Obesity is associated with increased mortality and risk of death is reduced with intentional weight loss.[8,9] Obesity is also associated with a number of chronic conditions, including hypertension, dyslipidemia, type 2 diabetes, gallstones, nonalcoholic fatty liver disease, sleep apnea, polycystic ovary syndrome (PCOS),[10,11] osteoarthritis,[12] coronary artery disease, stroke, heart failure, and certain cancers.[10,11] Additionally, there is significant psychosocial stigma and reduced quality of life associated with being obese.[13,14] In the US, the health care costs associated with obesity related conditions have increased to almost 10% of total health care expenditures and billions of dollars in direct and indirect costs.[15]

Clinical studies and epidemiological evaluations have suggested that moderate weight loss (approximately 5% to 10% reduction from baseline body weight) reduces total mortality and premature death from cardiovascular disease and diabetes in diabetic subjects[16] and reduces the risk of developing type 2 diabetes,[17,18] hypertension[19,20] and obstructive sleep apnea.[21] In addition, weight reduction has been shown to lower blood

pressure,[22,23] improve insulin sensitivity and glycemic control,[24,25] and improve lipid parameters.[26]

Obesity guidelines currently recommend that drug therapy be considered, in conjunction with nonpharmacological therapy, for subjects with a BMI of 30 kg/m^2 or greater or a BMI of 27 to 30 kg/m^2 with one or more obesity-related disorders.[27]

Sibutramine is one of only 2 drugs currently approved in the US as long-term treatment for weight management when lifestyle modification alone is unsuccessful.

4.0 Sibutramine

4.1 Regulatory History of Sibutramine

The original new drug application (NDA) for Meridia (sibutramine hydrochloride monohydrate) was submitted to the Food and Drug Administration (FDA) in August 1995, and reviewed at an FDA Advisory Committee meeting in September 1996. The FDA approved Meridia on 22 November 1997 for the treatment of obesity.

Sibutramine was approved in Germany in 1999 and subsequently in the other European Union (EU) member states. The drug was ultimately approved for sale in 92 countries.

At the time the pivotal trials were conducted for sibutramine, no regulatory guidance documents for evaluation of weight loss drugs were available; however, by the time sibutramine was approved in the US for the treatment of obesity, guidance documents for weight loss products had been issued in the US (draft, 1996) and the EU (1997). Sibutramine met the criteria for effectiveness in these Guidances at the time of approval, for weight loss and beneficial impact on secondary endpoints (improvement in TG and HDL-C) and also meets the effectiveness criteria for weight loss as stated in the current draft US (2007) and current EU (2008) obesity guidance documents.

Meridia is indicated in the US for use in the obese or overweight population (in the presence of other risk factors) and the US label summarizes the pertinent efficacy data. Additionally, on the basis of blood pressure and pulse findings in the clinical development program, the originally-approved Meridia labeling: 1) strongly warned against the use of the drug in patients with coronary artery disease and stroke, and 2) conveyed the need to monitor blood pressure and pulse.

Five years following US approval, in 2002, a subsequent comprehensive review of the safety of sibutramine was performed by the FDA following the temporary suspension of sibutramine in Italy over concerns about cardiovascular safety. In parallel, the European regulatory authorities also performed a review of the safety and benefit/risk of sibutramine under an Article 31 procedure, resulting in the reinforcement of a previous

postapproval commitment to perform a cardiovascular outcomes study with sibutramine. As a result of the FDA review, the US label was revised, the patient package insert was strengthened, and a risk management plan was approved, which incorporated a Dear Health Care Provider (DHCP) letter and a Dear Pharmacist letter reinforcing the appropriate prescribing information for sibutramine.

The SCOUT study, fulfilling the EU outcomes study postapproval commitment, was conducted from 2002-2009. The initial results of the study became available in November 2009, and were promptly communicated to regulatory authorities, including the FDA.

In January 2010, on the basis of their review of the preliminary results from SCOUT, the European CHMP recommended that the marketing authorizations for all sibutramine-containing medicinal products be suspended. Abbott promptly complied with this recommendation. The European Commission issued their final decision formally adopting the CHMP recommendation on 06 August 2010.

In January 2010, Abbott added to the labeling, with FDA agreement, a contraindication for the use of Meridia in patients with a history of cardiovascular disease. Abbott also submitted a Risk Evaluation and Mitigation Strategy (REMS) for Meridia with a Medication Guide in April 2010; this submission was approved on 04 August 2010.

4.1.1 Sibutramine Indication and US Label

According to the current US label[28] (Appendix A), sibutramine is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. Sibutramine is recommended for obese subjects with an initial BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).

The recommended starting dose of sibutramine is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after 4 weeks to a total of 15 mg once daily. Doses above 15 mg daily are not recommended.

The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose once daily. The US label advises that blood pressure and pulse changes should be taken into account when making decisions regarding dose titration.

The US label also advises that the safety and effectiveness of sibutramine, as demonstrated in randomized, double-blind, placebo-controlled trials, have not been determined beyond 2 years at this time.

Table 1. Key Elements of Meridia US Labeling

Indication	For weight loss and maintenance of weight loss in patients with BMI > 30 kg/m^2, or > 27 kg/m^2 in the presence of other risk factors, used in conjunction with a reduced calorie diet
Age	Adults < 65 years old
Blood pressure/Pulse	Contraindication for inadequately controlled hypertension of ≥ 145/90 mmHg. Measure blood pressure and pulse prior to starting therapy and monitor at regular intervals thereafter. The dose should be reduced or therapy should be discontinued in patients with sustained increases in blood pressure or pulse
Cardiovascular disease	Contraindication for coronary artery disease (e.g., angina, history of myocardial infarction), congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischemic attack [TIA])
Treatment duration	Up to 2 years

4.1.2 Scheduling

At the time of the original NDA approval the US Drug Enforcement Agency (DEA) and FDA classified sibutramine as a Schedule IV controlled substance due to its centrally-acting mechanism of action and concerns about abuse potential. In December 1999, Knoll Pharmaceutical Inc. (the original sponsor) filed a petition with DEA seeking to decontrol sibutramine, and Abbott updated that filing in October 2005. The 2005 update to the petition contained substantial preclinical, clinical, and postmarketing surveillance data supporting sibutramine's lack of abuse potential. Pending FDA's review, Meridia remains a Schedule IV controlled substance in the US.

4.1.3 Mechanism of Action

Sibutramine hydrochloride monohydrate (sibutramine) is a neuropharmacological drug that exerts central (CNS) and peripheral effects including norepinephrine and serotonin (5-HT) re-uptake inhibition.[29]

Sibutramine has a number of effects on body weight. It acts centrally to reduce energy intake by inducing a feeling of fullness (satiety) upon eating and leads to reduced food intake.[30,31] Sibutramine also increases energy expenditure (via increased thermogenesis), which limits the decline in metabolic rate that normally accompanies weight loss.[32,33]

As noted, sibutramine exerts both CNS and peripheral effects. In the CNS, norepinephrine transporter blockade attenuates sympathetic outflow through activation of alpha-2-adrenergic receptors and this central, sympatholytic effect may counteract the peripheral sympathetic stimulation.[34] This mechanism may explain why sibutramine increases the ratio of norepinephrine/adrenaline plasma level in normal healthy subjects and reduces this ratio in obese and essential hypertensive subjects.[35] It may also explain why in humans administration of sibutramine reduces sympathetic response to autonomic tests (tilt-table, cold pressor test) as well as direct microneurographic recordings of muscle sympathetic nerve activity.[34,36]

4.2 Sibutramine Clinical Trials

The original US NDA was submitted in 1995 and included data from 12 randomized-controlled studies of 1,871 sibutramine and 600 placebo-treated subjects; one of these 12 studies had a treatment period of 12 months (Appendix B).

Since the US approval of sibutramine in 1997, a substantial number of additional company-sponsored studies have been conducted to assess the weight loss effect of sibutramine in conjunction with diet and exercise. These studies were conducted across different countries and races in obese and overweight subjects with a range of comorbidities.

An integrated clinical trials (ICT) database, consisting of Abbott-sponsored studies submitted with the original NDA and those conducted following approval, has been compiled to allow for further characterization of the safety and efficacy of sibutramine in a population consistent with the US label for Meridia. Various subsets of clinical trials from the ICT database have been analyzed for specific safety or efficacy assessments. A summary of the ICT database and the subset of studies used in the different efficacy and safety assessments are provided in Appendix C.

4.3 Sibutramine Effects on Weight Management

4.3.1 Weight Loss Efficacy in US Registration Program

At the time of the original NDA, the efficacy of sibutramine as a weight loss agent was demonstrated in accordance with the FDA 1996 Draft Guidance for the Clinical Evaluation of Weight-Control Drugs.[37] Sibutramine continues to meet FDA weight loss criteria as defined in the Guidance, which was revised in 2007.[1]

In the clinical development program, sibutramine was given in conjunction with a range of diet and exercise regimens and was consistently shown to promote greater weight loss than diet and exercise alone.

In the original NDA, weight loss results were summarized using results from a meta-analysis of the 4 placebo-controlled non-diabetes studies conducted in obese subjects across multiple doses (5 to 30 mg) and a range of study durations (3 to 12 months).

Analyses of these data limited to sibutramine doses of 10 mg and 15 mg evaluated 801 sibutramine-treated subjects and 420 placebo-treated subjects; the majority were female (82%) and white (91%), with a mean age of 41.6 years and mean BMI of 32.1 kg/m^2.

Results from these analyses for the approved doses demonstrated significantly greater efficacy of sibutramine compared with placebo:

- Median weight loss in the range of 3.7 to 4.4 kg (difference from placebo)
- Mean percent weight loss in the range of 4.2% to 5.4% (difference from placebo)
- Approximately 15% to 20% more weight loss responders (defined as ≥ 5% weight loss) in the sibutramine group as compared to the placebo group.

In general, weight loss observed early in the course of treatment with sibutramine is predictive of patients who lose weight longer term. In a published meta-analysis of seven 12-month placebo-controlled diabetic or non-diabetic studies evaluating 10 mg or 15 mg of sibutramine, weight loss of at least 4 kg at 3 months was shown to have a positive predictive value of at least 84% for being a 5% weight loss responder at 1 year. Weight loss of less than 4 kg had a negative predictive value of at least 70% for being a 5% weight loss responder at 1 year.[38]

Labels for sibutramine globally reflect the need to monitor for weight loss early during treatment, and recommend adjusting or discontinuing sibutramine therapy on the basis of inadequate weight loss response.

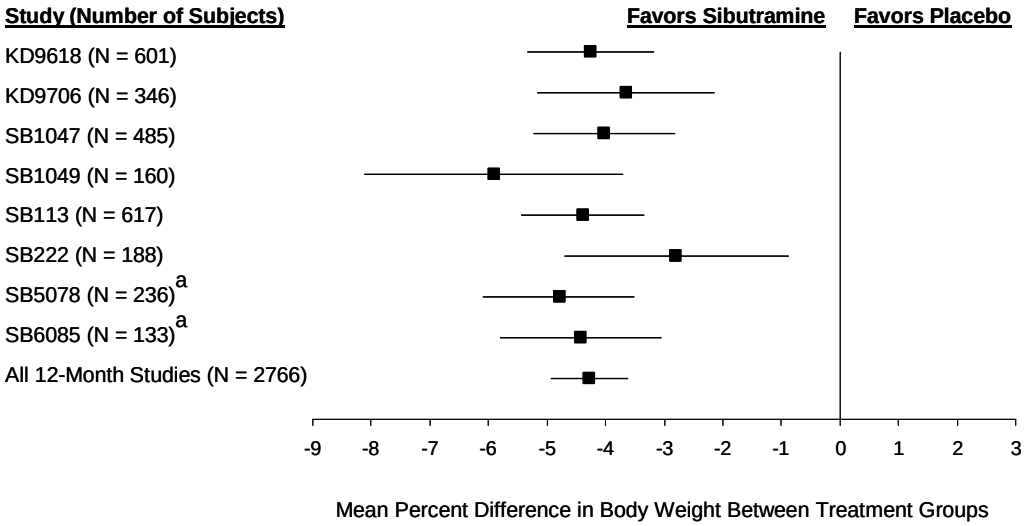
4.3.2 Integrated Analysis of Weight Loss Efficacy from Controlled Clinical Trials

An analysis of weight loss efficacy was conducted using selected studies from the ICT database (Appendix C). This meta-analysis included 8 randomized, double-blind, placebo-controlled studies that examined the effects of the most commonly used approved doses (10 mg and 15 mg) of sibutramine in the on-label population over a 12-month period.

The ICT weight loss cohort contains a total of 1,670 sibutramine-treated subjects (10 mg and 15 mg treatment groups combined) and 1,096 placebo-treated subjects.

Mean percent weight change across each of the 8 placebo-controlled studies consistently favored treatment with sibutramine over that of placebo (Figure 1).

Figure 1. Summary of the Difference in Mean Percent Weight Change at Month 12 by Study for the ICT Weight Meta-Analysis: LOCF



a. Subjects had diabetes mellitus.

Note: Number of subjects for each study include both placebo and sibutramine treatment groups.

The ICT weight meta-analysis:

- Confirmed greater mean absolute and percentage weight loss in the sibutramine group compared with the placebo group;
  - 4.08 kg and 4.28% difference from placebo at Month 12 (Table 2).
- Demonstrated greater percentages of sibutramine-treated subjects achieved ≥ 5%, ≥ 10%, and ≥ 15% body weight reduction compared to placebo-treated subjects:
  - 26.5%, 14.7%, and 7.6%, difference from placebo at Month 12 (Table 2).

Table 2. Summary of Weight Change/Loss Results at Month 12 from the ICT Weight Meta-Analysis: LOCF

	Month 12		
Mean Change from Randomization	**Placebo N = 1096**	**Sibutramine N = 1670**	**Treatment Difference**
Absolute, kg	–0.79	–4.87	–4.08*
Percent	–0.69	–4.97	–4.28*
5% weight loss responders	217 (19.8%)	774 (46.3%)	26.5%*
10% weight loss responders	88 (8.0%)	380 (22.8%)	14.7%*
15% weight loss responders	30 (2.7%)	173 (10.4%)	7.6%*

* Statistically significant at the 0.05 level.

Note: Mean weight at baseline was 94.93 kg in the sibutramine group and 95.01 kg in the placebo group.

Further examination of the weight loss data revealed that 126/217 (58.1%) of the placebo-treated subjects and 594/774 (76.7%) of the sibutramine-treated subjects who achieved 5% weight loss at 12 months had achieved this degree of weight loss by 3 months of treatment. This finding supports that a 3-month course of sibutramine is adequate to determine response to the weight loss effect of sibutramine treatment.

According to the 2007 (current) FDA Draft Guidance for Industry, "Developing Products for Weight Management,"[1] a weight loss drug is considered effective if, after 1 year of treatment, either of the following criteria is satisfied:

- The difference in mean weight loss between the active-product and placebo-treated groups is at least 5% and the difference is statistically significant
- The percentage of subjects who lose ≥ 5% of baseline body weight (5% responders) in the active-product group is at least 35%, is approximately double the percentage in the placebo-treated group, and the difference between groups is statistically significant.

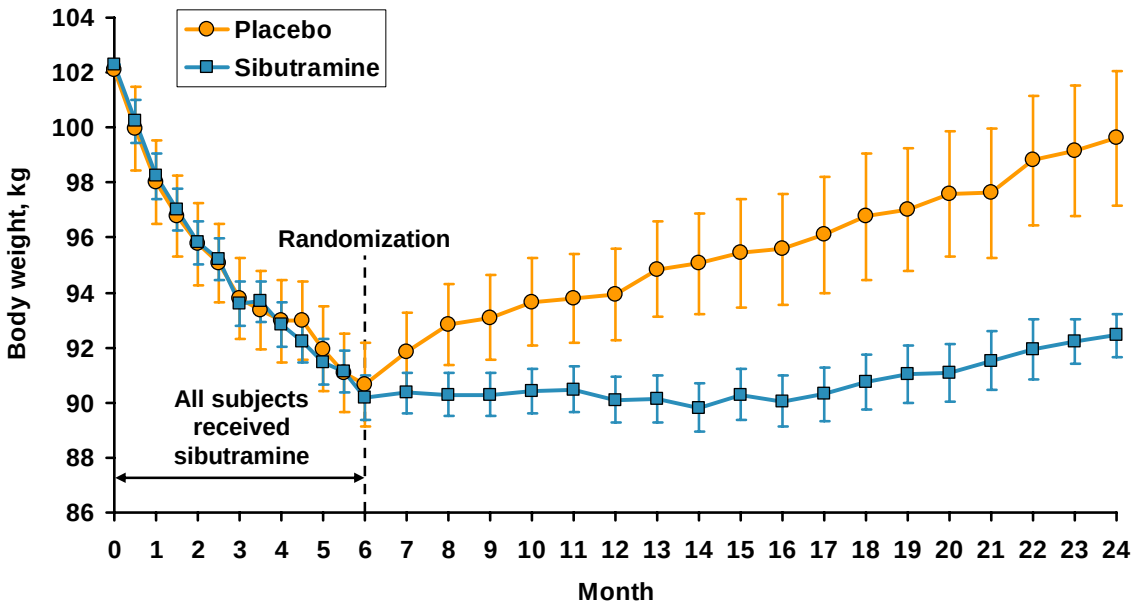
The results from the ICT weight meta-analysis meet the FDA's current 5% responder criterion and confirm the findings from the original NDA meta-analysis that

demonstrated clinically relevant weight loss is achieved with sibutramine treatment at the currently approved doses.

4.4 Sibutramine Effect on Weight Maintenance

Maintenance of weight loss with sibutramine is summarized in the US label, describing the results from a 2-year, double-blind, placebo-controlled trial.[28,39] After a 6-month run-in period during which all subjects received sibutramine 10 mg in conjunction with diet and exercise (mean weight loss, 26 lbs [11.9 kg]), subjects who lost ≥ 5% of their baseline weight entered the 18-month, double-blind, placebo-controlled treatment period and were randomized to sibutramine (10 to 20 mg, 352 subjects) or placebo (115 subjects) in addition to diet and exercise. The mean weight loss from initial body weight to endpoint was 21 lbs (9.5 kg) and 12 lbs (5.4 kg) for sibutramine- and placebo-treated subjects, respectively. Mean body weight during the study is shown for observed cases in Figure 2.

Figure 2. Mean Body Weight During Study: Observed Cases



Number of observations	Baseline	Month 6	Month 12	Month 18	Month 24
Placebo	115	115	94	69	57
Sibutramine	352	352	297	243	206

A statistically significantly ($P < 0.001$) greater percentage of sibutramine-treated subjects maintained at least 80% of their initial weight loss (i.e., after the 6-month run-in period) at 12, 18, and 24 months compared with placebo-treated subjects (Table 3).

Table 3. Percentage of Subjects Maintaining >= 80% of Initial Weight Loss at Each Time Point

Double-blind Treatment	Placebo	Sibutramine	*P* value
Month 12	38%	75%	< 0.001
Month 18	23%	62%	< 0.001
Month 24	16%	43%	< 0.001

Also, greater percentages of sibutramine-treated subjects lost ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20% of their initial body weight at endpoint (Table 4).

Table 4. Percentage of Subjects Achieving at Least 5%, 10%, 15%, and 20% Weight Loss at Endpoint

	Treatment in Double-blind Period	
Percentage of Initial Body Weight Lost	**Placebo N = 115**	**Sibutramine N = 352**
≥ 5%	49%	67%
≥ 10%	19%	37%
≥ 15%	5%	17%
≥ 20%	3%	9%

4.5 Sibutramine Effects on Obesity-Related Comorbidities

It has been well established that weight reduction improves obesity-related comorbidities. According to the current 2007 Draft FDA Guidance, "Improvements in blood pressure, lipids, glycemia or other areas commensurate with the degree of weight lost are expected in subjects treated with an effective weight-management product. Therefore, changes in weight-related comorbidities should be factored into the efficacy assessment of investigational weight-management products."

4.5.1 Sibutramine Effects on Lipid Endpoints

In the NDA, the effects of sibutramine on lipids were summarized using results from a meta-analysis of the 11 studies conducted in both diabetic and non-diabetic obese subjects across multiple doses (1 to 30 mg). Of note, only 2 of these studies included fasted laboratory assessments.

This lipid meta-analysis (1996 NDA) supported the approval of sibutramine and showed statistically significant improvements in TG and HDL-C in the sibutramine group compared with the placebo group (Table 5).

Compared to the overall groups, the sibutramine and placebo 5% weight loss responders had greater improvements in TG and HDL-C, and there were no clinically meaningful differences between the treatment groups, indicating that weight loss with sibutramine was associated with similar changes as nonpharmacologically-induced weight loss.

Table 5. Mean Percent Changes in Lipids at Endpoint from the 1996 NDA Lipid Meta-Analysis: LOCF

	Mean Percent Change			
Category	**Triglycerides**	**Total Cholesterol**	**LDL-C**	**HDL-C**
All placebo	0.48 (N = 475)	–1.60 (N = 475)	–0.15 (N = 233)	–0.58 (N = 248)
< 5% weight loss	4.46 (N = 382)	–0.51 (N = 382)	0.62 (N = 205)	–0.77 (N = 217)
≥ 5% weight loss	–15.28 (N = 92)	–6.27 (N = 92)	–6.22 (N = 27)	0.94 (N = 30)
All sibutramine	–8.03*** (N = 1415)	–2.22 (N = 1416)	–2.14 (N = 844)	3.98*** (N = 867)
< 5% weight loss	0.36 (N = 693)	–0.05 (N = 694)	–0.70 (N = 432)	2.56 (N = 444)
≥ 5% weight loss	–16.61 (N = 717)	–4.92 (N = 717)	–5.13 (N = 407)	5.07 (N = 418)

LOCF = last observation carried forward (through last on-treatment assessment); LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol

*** Statistically significant difference between placebo and sibutramine at the 0.001 level.

An analysis of effects on lipids was conducted using selected studies from the ICT database (Appendix C). The ICT lipid meta-analysis set included 7 studies that were at least 12 months in duration with fasted lipid levels. The ICT lipid meta-analysis

evaluated 1,355 subjects treated with sibutramine (10 mg and 15 mg doses combined) compared with 942 subjects receiving placebo. The subject demographics and exposures were similar to those from the 1996 NDA lipid meta-analysis.

Results from the ICT lipid meta-analysis are similar to those seen previously with respect to TG and HDL-C and confirmed the statistically significant improvements in these parameters in the sibutramine group (Table 6). A review of the 7 individual studies demonstrated consistent improvements with sibutramine in TG and HDL-C as compared to placebo. Changes in LDL-C and total cholesterol (TC), however, were variable between the individual 7 studies, with the overall mean changes showing a small increase in the sibutramine group as compared to the placebo group for these parameters.

In the sibutramine and placebo 5% weight loss responders, there were greater improvements in TG and HDL-C, and changes were similar between the treatment groups, indicating that weight loss with sibutramine was associated with similar changes as nonpharmacologically-induced weight loss. Small increases in LDL-C and TC were noted in the sibutramine group, as compared to placebo.

Table 6. Mean Percent Changes in Lipids at Endpoint from the ICT Lipid Meta-Analysis: LOCF

	Mean Percent Change			
Category	**Triglycerides**	**Total Cholesterol**	**LDL-C**	**HDL-C**
All placebo	13.03 (N = 871)	6.17 (N = 871)	4.59 (N = 862)	10.28 (N = 866)
< 5% weight loss	15.09 (N = 714)	6.53 (N = 714)	5.17 (N = 706)	9.14 (N = 709)
≥ 5% weight loss	–0.06 (N = 156)	5.29 (N = 156)	2.59* (N = 155)	16.96 (N = 156)
All sibutramine	4.61** (N = 1280)	6.47 (N = 1280)	5.81 (N = 1268)	16.00** (N = 1275)
< 5% weight loss	12.20 (N = 675)	6.65 (N = 675)	4.85 (N = 669)	13.07* (N = 672)
≥ 5% weight loss	–4.16 (N = 605)	7.88 (N = 605)	9.66 (N = 599)	19.06 (N = 603)

LOCF = last observation carried forward; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol

*,** Statistically significant difference between placebo and sibutramine at the 0.05 and 0.01 level, respectively.

4.5.2 Sibutramine Effects on Glycemic Endpoints in Subjects with Type 2 Diabetes Mellitus

Analyses in overweight and obese diabetic subjects previously submitted to FDA showed no statistically significant differences in measures of glycemic control between sibutramine- and placebo-treated subjects.

- Mean change in glucose (mg/dL): sibutramine –2.3, placebo 4.3
- Mean change in HbA_{1c} (%): sibutramine –0.29, placebo –0.15

An analysis of sibutramine effects on glycemic endpoints was conducted using two 12-month studies from the ICT database (Appendix C). The 2 studies collected fasted laboratory samples in overweight and obese diabetic subjects treated with an on-label dose (15 mg) (sibutramine N = 183, placebo N = 186). Results were similar to those from previously reported analyses, with no clinically meaningful differences between treatment groups for changes in fasting glucose or HbA_{1c} (Table 7).

In the sibutramine and placebo 5% weight loss responders, improvements in glucose and HbA_{1c} were observed with no clinically meaningful differences between the treatment groups, indicating that weight loss with sibutramine was associated with similar changes in glucose or HbA_{1c} as nonpharmacologically-induced weight loss.

Table 7. Mean Percent Change in Fasting Glucose and Mean Change in HbA_{1c} at Endpoint from the ICT Meta-Analysis: LOCF

	Month 12		
Variable	**Placebo**	**Sibutramine**	**Difference**
Mean percent change in glucose			
All subjects	1.22 (N = 185)	0.46 (N = 181)	–0.76
≥ 5% weight loss	–6.24 (N = 29)	–5.61 (N = 99)	0.63
Mean change in HbA_{1c}, %			
All subjects	–0.09 (N = 178)	–0.34 (N = 173)	–0.25
≥ 5% weight loss	–0.56 (N = 28)	–0.75 (N = 97)	–0.19

Notes: Mean baseline fasting glucose and HbA_{1c} were 161.13 mg/dL and 8.08%, respectively, in the placebo group and 160.58 mg/dL and 8.17%, respectively, in the sibutramine group.

≥ 5% weight loss is defined from randomization baseline to Month 12.

4.5.3 Sibutramine Effects on Metabolic Syndrome

Sibutramine's effects on the incidence of metabolic syndrome were assessed as a means to describe the drug's effect across multiple parameters. In this analysis metabolic syndrome was defined as meeting 3 or more of the following 5 criteria:[40]

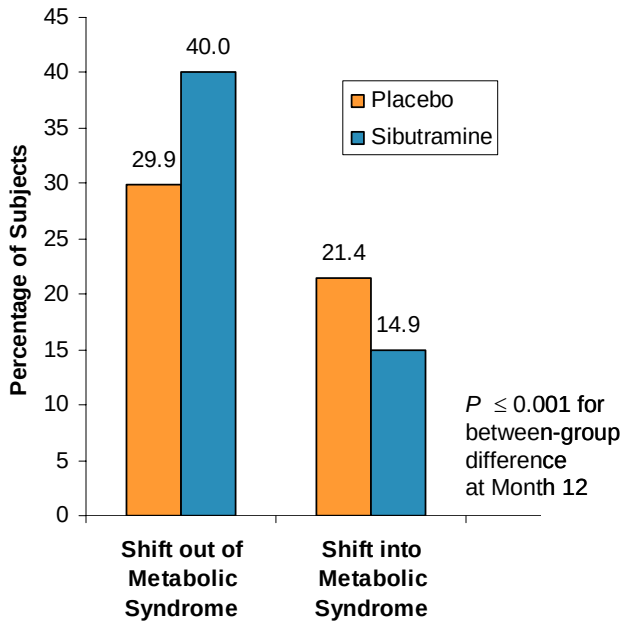
- Abdominal obesity (waist circumference > 102 cm/> 40 in [men] or > 88 cm/> 35 in [women])
- Elevated triglycerides (≥ 150 mg/dL)
- Decreased HDL-C (< 40 mg/dL [men] or < 50 mg/dL [women)
- Elevated blood pressure (≥ 130/≥ 85 mmHg)
- Elevated fasting glucose (≥ 110 mg/dL)

The analysis of sibutramine effects on metabolic syndrome was conducted using selected studies from the ICT database (Appendix C). The ICT metabolic syndrome meta-analysis set included five 12-month, non-diabetes studies for which all of the metabolic syndrome criteria listed above were reported and for which fasted laboratory samples were collected from obese subjects (sibutramine N = 1,172; placebo N = 756).

Subjects were categorized as those who did or did not meet metabolic syndrome criteria. At baseline the percent of subjects who met criteria for metabolic syndrome was 42.0% and 41.9% in the placebo and sibutramine groups, respectively.

The results of the shift analysis for metabolic syndrome showed an improvement with sibutramine treatment since a greater percentage of sibutramine-treated subjects than placebo-treated subjects had shifted out of metabolic syndrome diagnosis at Month 12 (40.0% [193/483] versus 29.9% [93/311]) and a smaller percentage of sibutramine-treated subjects than placebo-treated subjects had shifted into metabolic syndrome diagnosis at Month 12 (14.9% [100/670] versus 21.4% [92/429]).

Figure 3. Shift in Metabolic Syndrome Diagnosis at Month 12 in the ICT Metabolic Syndrome Meta-Analysis Set: LOCF



Importantly, review of the individual blood pressure criterion showed that the percentage of subjects with baseline blood pressure below 130/85 mmHg who shifted to a blood pressure ≥ 130/85 mmHg was similar between the groups (23.5% for placebo group and 25.1% for sibutramine group).

4.5.4 Other Clinical Effects of Sibutramine

The impact of sibutramine on a range of weight-related comorbidities was investigated in post-registration clinical studies. Results suggested that weight reduction with sibutramine improved sleep-disordered breathing and symptoms in subjects with obstructive sleep apnea,[41] improved the metabolic and reproductive abnormalities that characterize PCOS in women of reproductive age,[42,43] and improved health-related quality of life.[44]

4.6 Safety of Sibutramine

4.6.1 Sibutramine Effects on Blood Pressure and Pulse Rate

The effects of sibutramine on blood pressure and pulse were fully investigated during the development program. The effects of sibutramine on blood pressure and pulse in a meta-analysis of 11 placebo-controlled studies were summarized in the NDA.

The results from the NDA meta-analysis for the sibutramine doses (5, 10, and 15 mg: N = 1,165) showed small mean increases compared to placebo (N = 592) in systolic blood pressure (SBP) (1.1, 1.5 and 2.2 mmHg, respectively) and diastolic blood pressure (DBP) (0.7, 1.7, and 1.7 mmHg, respectively). The meta-analysis mean changes for the sibutramine doses of 10 mg and 15 mg are presented in Table 8.

Sibutramine-treated subjects with at least 5% weight loss (5% weight loss responders), showed slight reductions in SBP and DBP; however, greater reductions were observed in the placebo-treated subjects with at least 5% weight loss. The reductions in SBP and DBP observed with sibutramine are not commensurate with those expected with the degree of weight loss achieved.

For pulse, the results showed small mean increases for sibutramine compared to placebo (3.7 to 3.8 bpm). In the sibutramine 5% weight loss responders group, pulse increases were similar to the all sibutramine-treated subjects. For placebo 5% weight loss responders, reduction in pulse was observed.

Table 8. Mean Changes in Blood Pressure and Pulse at Endpoint from the 1996 NDA Meta-Analysis: LOCF

Variable	Mean Change			Mean Change		
	Placebo	Sibutramine 10 mg	Treatment Difference	Placebo	Sibutramine 15 mg	Treatment Difference
SBP, mmHg						
All subjects	–2.1 (N = 515)	–0.6 (N = 527)	1.5	–0.2 (N = 405)	2.0 (N = 416)	2.2
≥ 5% weight loss	–6.2 (N = 99)	–2.2 (N = 247)	4.0	–4.1 (N = 61)	1.0 (N = 207)	5.1
DBP, mmHg						
All subjects	–1.4 (N = 515)	0.3 (N = 527)	1.7	–0.2 (N = 405)	1.5 (N = 416)	1.7
≥ 5% weight loss	–3.2 (N = 99)	–0.9 (N = 247)	2.3	–2.0 (N = 61)	1.1 (N = 207)	3.1
Pulse rate, bpm						
All subjects	–0.6 (N = 515)	3.2 (N = 527)	3.8	0.5 (N = 405)	4.2 (N = 415)	3.7
≥ 5% weight loss	–2.5 (N = 99)	3.4 (N = 247)	5.9	–2.0 (N = 61)	3.9 (N = 207)	5.9

LOCF = last observation carried forward (through last on-treatment assessment)

Sustained increases in blood pressure of potential clinical significance were assessed in the single 12-month registration study (SB 1047). More sibutramine-treated subjects than placebo-treated subjects experienced sustained increases in blood pressure of potential clinical significance, defined as SBP or DBP ≥ 10 mmHg above baseline on 2 consecutive study visits (described as "outliers") (Table 9).

Table 9. Percentage of Subjects with 2 Consecutive Elevations over Baseline Blood Pressure Through Month 3 During the 12-Month Registration Study

	2 Consecutive Elevations of ≥ 10 mmHg over Baseline, N (%)	
Variable	**Placebo (N = 163)**	**Sibutramine (10 and 15 mg groups combined) (N = 322)**
SBP	56 (34%)	131 (41%)
DBP	26 (16%)	90 (28%)

Importantly, the majority (approximately 60%) of subjects destined to have potentially clinically significant elevations in blood pressure could be identified early (within the first 3 study visits, i.e., after 1 or 2 months of treatment). The finding that these subjects can be identified early indicates that these criteria could be used to determine which patients should be discontinued from treatment after a short (3-month) course of sibutramine.

Greater mean decreases in SBP or DBP were seen in sibutramine-treated subjects when outliers (as defined above) were excluded (Table 10).

Table 10. Mean Blood Pressure Changes at Endpoint in the 12-Month Registration Study Including and Excluding Blood Pressure Outliers: LOCF

	Placebo		Sibutramine 10 mg		Sibutramine 15 mg	
	Baseline (N)	Change from Baseline	Baseline (N)	Change from Baseline	Baseline (N)	Change from Baseline
SBP, mmHg						
Including outliers[a]	128.4 (N = 163)	–0.4	129.8 (N = 161)	1.6	130.3 (N = 161)	1.8
Excluding outliers[a]	131.5 (N = 116)	–4.6	133.1 (N = 113)	–3.1	133.0 (N = 113)	–3.7
DBP, mmHg						
Including outliers[a]	81.7 (N = 163)	–1.9	80.8 (N = 161)	0.8	80.5 (N = 161)	0.5
Excluding outliers[a]	82.9 (N = 116)	–3.5	82.4 (N = 113)	–0.9	82.2 (N = 113)	–1.9

LOCF = last observation carried forward (through last on-treatment assessment)

a. Placebo- or sibutramine-treated subjects who had an increase in SBP or DBP of at least 10 mmHg at 2 consecutive visits by Month 2.

An analysis of the effects of sibutramine on blood pressure and pulse was conducted using selected studies from the ICT database (Appendix C).

The ICT vital signs meta-analysis set included 28 studies. A total of 3,312 sibutramine-treated subjects and 2,316 placebo-treated subjects were included in the analysis set. Overall, the majority of subjects were female (77.6%) and white (92.6%). The mean age of the subjects was 44.0 years and mean BMI was 33.42 kg/m^2.

The sibutramine and placebo groups were generally similar at baseline; mean SBP was 127 mmHg for the sibutramine group and 129 mmHg for the placebo group, DBP was 80 and 81 mmHg for the respective treatment groups, and pulse was 74 bpm for both of the treatment groups.

The results from the ICT vital signs meta-analysis are similar to those from the registration program. Small mean increases in SBP and DBP (1.6 mmHg and 2.2 mmHg, respectively, at Month 12) were seen in sibutramine-treated subjects compared to placebo-treated subjects. For 5% weight loss responders, sibutramine-treated subjects generally had smaller mean increases in SBP and DBP compared to all sibutramine-treated subjects; however, mean reductions were seen in placebo-treated subjects (Table 11).

For pulse, the ICT meta-analysis results showed a small mean increase for sibutramine compared to placebo at Month 12 of 3.6 bpm. The mean change in pulse was similar in sibutramine 5% weight loss responders (4.7 bpm) compared to 4.6 bpm in all sibutramine-treated subjects at Month 12 (Table 11).

Table 11. Mean Changes in Blood Pressure and Pulse in the ICT Vital Signs Meta-Analysis

	Month 3 Mean Change			Month 6 Mean Change			Month 12 Mean Change		
Vital Sign	**PBO**	**SBT**	**DIFF**	**PBO**	**SBT**	**DIFF**	**PBO**	**SBT**	**DIFF**
SBP, mmHg									
All subjects	–0.9 (N = 1959)	–0.4 (N = 2929)	0.5	0.4 (N = 1181)	0.8 (N = 1953)	0.4	0.3 (N = 681)	1.9 (N = 1098)	1.6*
≥ 5% responders[a]	–3.4 (N = 430)	–1.4 (N = 1464)	2.0	–2.9 (N = 299)	–0.3 (N = 1074)	2.5	–3.2 (N = 167)	0.4 (N = 611)	3.5*
DBP, mmHg									
All subjects	–0.9 (N = 1959)	0.5 (N = 2929)	1.4***	–0.5 (N = 1181)	1.3 (N = 1953)	1.8***	–0.8 (N = 681)	1.4 (N = 1098)	2.2***
≥ 5% responders	–1.3 (N = 430)	0.1 (N = 1464)	1.4	–1.7 (N = 299)	0.7 (N = 1074)	2.4*	–3.3 (N = 167)	0.5 (N = 611)	3.9*
Pulse, bpm									
All subjects	–0.5 (N = 1955)	3.8 (N = 2923)	4.3***	0.5 (N = 1181)	4.4 (1952)	3.9***	1.0 (N = 681)	4.6 (N = 1097)	3.6***
≥ 5% responders	–1.7 (N = 428)	3.8 (N = 1460)	5.5***	–0.1 (N = 299)	4.6 (N = 1074)	4.7***	–1.3 (N = 167)	4.7 (N = 611)	6.0***

bpm = beats per minute; DIFF = point estimate of difference between sibutramine and placebo groups; PBO = placebo; SBT= sibutramine

*,**,*** Significant at the 0.05, 0.01, and 0.001 levels, respectively.

a. Responders lost 5% of body weight from Lead-in Period Baseline at the month specified.

Note: *P* value for difference between treatment groups in mean change from randomization baseline using a contrast within the ANOVA model with effects for treatment, study, and treatment*study interaction.

Sustained increases in blood pressure of potential clinical significance, previously defined as SBP or DBP increases ≥ 10 mmHg above baseline on 2 consecutive study visits, were also seen in a greater percentage of sibutramine-treated subjects compared to placebo-treated subjects in the ICT vital signs meta-analysis (Table 12). Importantly, the majority (approximately 70%) of these sibutramine blood pressure outliers were identified by Month 3. The finding that these subjects can be identified early provides further support that these criteria could be used to determine which patients should be discontinued from treatment after a short (3-month) course of sibutramine.

Likewise, sustained increases in pulse of potential clinical significance, defined as increases ≥ 10 bpm above baseline on 2 consecutive study visits, were seen in a greater percentage of sibutramine-treated subjects compared to placebo-treated subjects (Table 12). Again, the majority (greater than 70%) of the sibutramine pulse outliers were identified by Month 3.

Table 12. Percentage of Subjects with >= 10 mmHg Increase from Baseline Blood Pressure or >= 10 bpm Increase from Baseline Pulse on 2 Consecutive Visits: ICT Studies at Least 12 Months in Duration

	Percentage by Month 3			Percentage by Month 12		
Vital Signs	**Placebo N = 1047**	**Sibutramine N = 1605[a]**	**Treatment Difference**	**Placebo N = 1047**	**Sibutramine N = 1605[a]**	**Treatment Difference**
SBP, mmHg	29.1	31.7	2.5	39.9	45.5**	5.6
DBP, mmHg	16.6	22.3***	5.7	22.9	30.2***	7.2
Pulse, bpm	19.0	31.0***	12.0	27.2	42.2***	15.0

bpm = beats per minute; treatment difference = point estimate of difference between sibutramine and placebo groups

a. N = 1604 at Months 3 and 12 for pulse.

,* Significant at the 0.01 and 0.001 levels, respectively.

Note: *P* values comparing treatment groups were based on Chi-square test.

4.6.2 Selected Adverse Events of Interest for Sibutramine

4.6.2.1 Placebo-Controlled Trials Conducted in Support of the US Registration

The most common adverse events occurring in greater than 10% of sibutramine-treated patients in the registration program were dry mouth, anorexia, insomnia, constipation, headache, and rhinitis.

In placebo-controlled obesity trials at the time of US registration, the following adverse events related to the cardiovascular system were more frequently associated with sibutramine therapy than placebo: palpitations, tachycardia, vasodilatation, and increased blood pressure. Their incidence ranged from 2.0% to 2.6% for sibutramine-treated patients compared to less than 1% for placebo-treated subjects.

4.6.2.2 Results from ICT Psychiatric Meta-Analysis and Pharmacovigilance Postmarketing Data

Assessments of cardiovascular adverse events observed in the ICT database and in pharmacovigilance data were performed and are presented in Section 6.0. Additionally, the ICT database and pharmacovigilance data have been analyzed for psychiatric events of interest. These findings are presented below. Obesity has been linked to a higher prevalence of psychiatric disorders and obese patients appear to be at higher risk for depression. Suicide events and psychiatric adverse events, therefore, are of interest in this disease setting. The US label *Adverse Events* section for Meridia notes that postmarketing cases of depression, psychosis, mania, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment.

The US label *Warning* section for Meridia includes class labeling regarding the risk of neuroleptic malignant syndrome (NMS) associated with use of selective serotonin reuptake inhibitors (SSRIs) and SNRIs. Additional safety information pertaining to the risk of Drug Abuse and Dependence is also included in the US label.

To further evaluate the risk of events in the population of obese subjects, 2 sources of information have been analyzed:

- An ICT analysis of sibutramine in obese subjects, and
- Pharmacovigilance postmarketing surveillance data

4.6.2.3 ICT Analysis for Psychiatric Events of Interest

Due to sibutramine's centrally-acting mechanism of action, an assessment of potential psychiatric safety issues was conducted. This analysis was performed using an ICT database containing information from 46 randomized placebo-controlled trials and an additional 22 open-label or non–placebo-controlled studies for the indicated population (Appendix B). This analysis provided safety experience for a total of 20,079 sibutramine-treated subjects. The psychiatric safety issues of interest were evaluated using relevant standardized MedDRA queries (SMQ).

The results of this analysis are summarized in Table 13.

Table 13. SMQs Related to Psychiatric Adverse Events of Interest: Placebo-Controlled and All Sibutramine On-Label Analysis Sets

	Placebo-Controlled Analysis Set		
SMQ	**Placebo N = 3491**	**Sibutramine N = 5812**	**All Sibutramine N = 20079**
Suicide/Self Injury			
No. of Subjects (%)	0	2 (< 0.1%)	4 (< 0.1%)
Events	0	2	4
E/100PY	0.000	0.051	0.040
HR (95% CI)	Not calculated[a]		
Drug Abuse			
No. of Subjects (%)	0	1 (< 0.1%)	1 (< 0.1%)
Events	0	1	1
E/100PY	0.000	0.025	0.010
HR (95% CI)	Not calculated[a]		
Depression			
No. of Subjects (%)	103 (3.0%)	195 (3.4%)	393 (2.0%)
Events	130	236	521
E/100PY	5.163	5.981	5.195
HR (95% CI)	1.103 (0.862–1.411)		
Psychosis and Psychotic Disorders			
No. of Subjects (%)	31 (0.9%)	85 (1.5%)*	169 (0.8%)
Events	32	105	232
E/100PY	1.271	2.661	2.313
HR (95% CI)	1.366 (0.893 – 2.090)		

a. The HR and the confidence interval were not calculated because of the low number of events.

* $P = 0.016$ comparing between placebo and sibutramine using Fisher's exact test.

Note: HR is for treatment effect by Cox proportional hazards modeling.

There were no cases of neuroleptic malignant syndrome (SMQ) identified in either the placebo-controlled or open-label studies. Also, there were no cases of completed suicide reported with sibutramine treatment. The single case of drug abuse (preferred term,

intentional overdose) reported for sibutramine was a duplicate event and represented an attempted suicide.

The incidence and event rate for depression appeared similar between placebo- and sibutramine-treatment. Of note, there were 3 sibutramine reports described as suicidal thoughts or ideation; however, as indicated previously, there were no reports of completed suicide.

There were significantly more reports of psychosis/psychotic disorders (SMQ) associated with sibutramine. The differential incidence rate was primarily attributable to reports of thinking abnormal. In general, these were nonserious reports describing difficulties with concentration or unclear thinking.

4.6.2.4 Postmarketing Experience

The Abbott Global Postmarketing Safety Database contains reports of adverse events, including spontaneously reported adverse events received directly from health care professionals and from the general public. Additional sources for adverse events include reports from the literature and adverse event reports from clinical trials or postmarketing surveillance studies. The limitations of postmarketing data are well recognized and include underreporting, bias as to which cases are selected for reporting, variable quality of the information in any particular case, and lack of precise numbers of subjects who undergo treatment.

There has been extensive postmarketing global experience with sibutramine including patient exposure estimated at over 6 million patient treatment-years (PTY); however, the above noted factors complicate the ability of postmarketing data to estimate a true incidence of any adverse event or to establish a definitive cause-effect relationship between the drug and an adverse event. Reporting rates (number of reports/100 PTY) are presented below.

To review the reported psychiatric adverse events with sibutramine in the "real-world setting," the Abbott safety database was searched for sibutramine cases entered from the

first regulatory approval of sibutramine (12 November 1997) through 20 May 2010, excluding cases derived from clinical trials. There were 2 areas of concentrated review: suicide and other neuropsychiatric events. These reviews are presented below. It is noted that assessment of individual reports of psychiatric events with sibutramine use is significantly confounded by the underlying obesity and prevalence of psychiatric disorders.

Suicide/Suicidal Ideation

There were 130 reports of suicide or related conditions (0.0021/100PTY) in the postmarketing experience; 7 reported a fatality (0.0001/100PTY).

- For context, data from a prospective cohort study of 46,755 men enrolled in the US Health Professionals Follow-Up Study beginning 1986 and followed until death or until February 2002 reported the mortality rate of suicide among obese males (BMI ≥ 30 kg/m^2) as 0.013 per 100 person-years.[45]

Depression

There were 1,214 reports of depression in the postmarketing experience. The reporting rate was 0.0195/100 PTY, which is lower than the 5.195 events/100 person-years for all sibutramine-treated subjects noted above from the clinical trials (Table 13).

Psychosis

There were 78 reports of psychosis in the postmarketing experience. The reporting rate was 0.0012/100 PTY, which is lower than the 2.313 events/100 person-years noted above from the clinical trials (Table 13).

Other Neuropsychiatric Events

An evaluation was conducted that focused on other neuropsychiatric events including panic attack, paranoia, hallucination, aggression, delusion, abnormal behavior, mental disorder, withdrawal syndrome, disorientation, and apathy. The report rates for these

types of events were very low and ranged from 0.0001/100 PTY (for disorientation and apathy) to 0.0002/100 PTY (for panic attack and paranoia).

4.6.2.5 Summary of Assessment of Psychiatric Events

Overall, on the basis of the ICT analysis, there were low numbers of events grouped under the Drug Abuse or Suicide/Self Injury SMQ with no events of completed suicide. For the Psychosis and Psychotic Disorders SMQ, reports with the preferred term of "thinking abnormal" were more often associated with sibutramine therapy. The current US label lists "thinking abnormal" as an adverse event reported in ≥ 1% of all subjects who received sibutramine in controlled and uncontrolled premarketing studies.

Analysis of these reports does not suggest an increased risk or safety signal for psychiatric events with the use of sibutramine.

5.0 Sibutramine Cardiovascular Outcomes Study (SCOUT)

5.1 Regulatory History - Development of the SCOUT Protocol

The European CHMP required Knoll to conduct SCOUT, a cardiovascular outcomes study, as a postapproval condition of marketing authorization.

The requirement originated with questions articulated during the Mutual Recognition Procedure (MRP) by the European regulators. Specifically, the Belgian regulatory authority expressed a concern that 1) sibutramine could increase blood pressure and pulse in a substantial number of users; and 2) the long-term consequences of these effects had not been sufficiently documented. In particular, the regulators asked whether sibutramine's effect on blood pressure and pulse could diminish or even nullify the positive effects of weight loss on cardiovascular health.

The SCOUT study design evolved over time, as Knoll and later Abbott discussed the feasibility of various study aspects and designs with an ad hoc protocol committee of the CHMP. Two main alternatives were discussed. The first would have investigated the use of sibutramine in subjects with impaired glucose tolerance, with a primary endpoint of progression to type 2 diabetes and secondary cardiovascular endpoints. The second proposal was for a CV outcomes study.

The ad hoc CHMP protocol committee selected the CV outcomes study design and required specific study design features to ensure that an adequate CV outcome event rate would be achieved. This was to ensure the feasibility of the study (i.e., that the study would not take too long or require an exceedingly large number of patients). These requisite design features included the following:

- Enrollment of older subjects at high risk for CV events (i.e., with a history of MI or stroke).
- Subject exposure to long-term treatment (up to 6 years), far greater than the standard 1 to 2 years of treatment.

- The continuation of treatment for all subjects, regardless of whether they experienced weight loss (to maintain balanced treatment arms), as opposed to the recommended practice of discontinuing therapy for inadequate weight loss.
- A 6-week Lead-in Period during which all subjects received sibutramine treatment, even those eventually randomized to the placebo group.

In July 2002, the CPMP reviewed the SCOUT protocol, with the changes intended to ensure an adequate POE rate, and agreed to the protocol as presented. The study was initiated in December 2002, and the first patient was enrolled in January 2003.

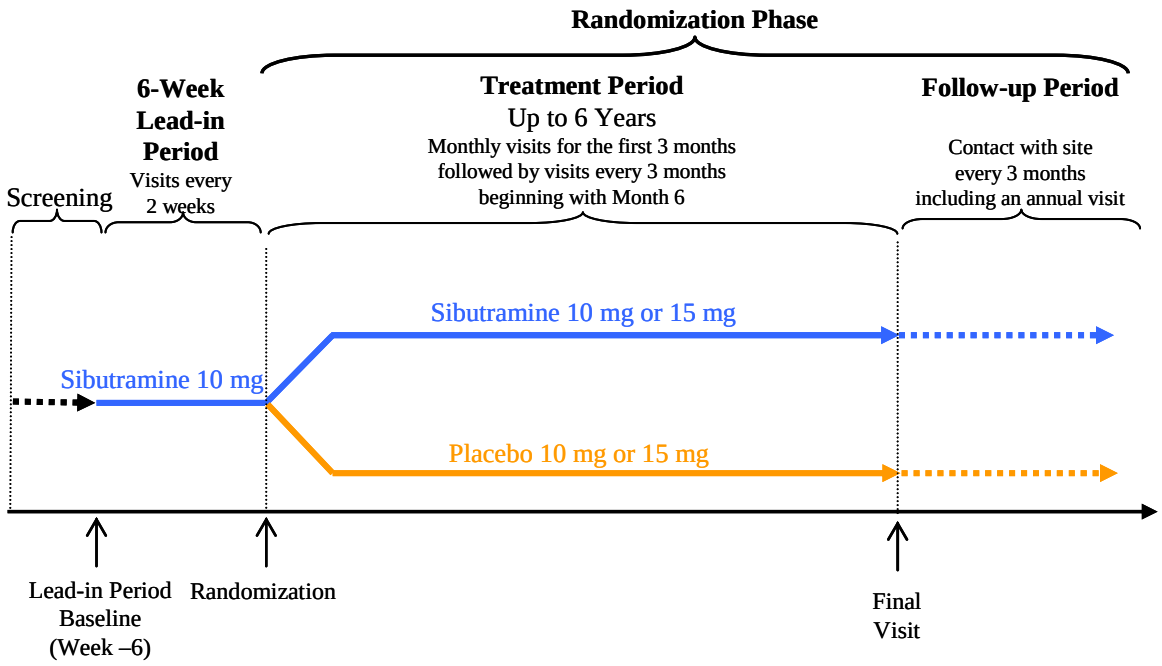
5.2 Study Background

5.2.1 Study Design

SCOUT was a randomized, double-blind, placebo-controlled, parallel-group, multinational, multicenter study with 4 periods (Figure 4) as follows:

1. A screening period
2. A 6-week single-blind sibutramine Lead-in Period
3. A randomized double-blind Treatment Period
4. A double-blind Follow-up Period for subjects who discontinued study drug.

Figure 4. SCOUT Study Schematic



Lead-in Period

SCOUT included a previously unstudied, high-CV-risk, largely contraindicated population. Therefore, as a safety precaution, the protocol included a 6-week, single-blind, Lead-in Period with the following features:

- Fixed dose of sibutramine (10 mg),
- No change in blood pressure medication allowed, and
- Monitoring every 2 weeks for changes in pulse, blood pressure, and weight, as well as adverse events.
  - Subjects who had increases in SBP and/or DBP of > 10 mmHg or in pulse of > 10 bpm at any 2 consecutive study visits during the Lead-in Period were not eligible for randomization.

All subjects received a cardioprotective diet and exercise management.

Randomization Phase

Following the 6-week, single-blind Lead-in Period during which all subjects received sibutramine 10 mg daily, eligible subjects entered the double-blind, placebo-controlled, Randomization Phase:

Monitoring:

- Anthropomorphic and vital sign measurements and concomitant medication use were collected monthly for the first 3 months and every 3 months thereafter for subjects on study medication and annually for subjects who discontinued study medication.
  - Concomitant medication information was based on medication class only (e.g., beta-blocker) for 6 specific conditions. Information about specific medication and changes in dose was not collected.
  - Study drug should have been discontinued in subjects who met any of the following criteria in the treatment period:
    - Mean pulse that remains at > 120 bpm, within 1 to 2 weeks following an initial mean heart rate of > 120 bpm.
    - Mean SBP > 180 mmHg and/or mean DBP > 115 mmHg, following down-titration of study medication (if applicable) and resistant to antihypertensive therapy.
    - Mean SBP remains > 160 mmHg and/or mean DBP remains > 100 mmHg following antihypertensive therapy and/or study drug dose reduction (after initially reaching an elevation of > 180/115 mmHg).
- Laboratory evaluations and electrocardiograms were performed annually.
- Serious adverse events, CV outcome events, and adverse events leading to discontinuation were collected throughout the study.

Study Drug Administration:

- Subjects were randomly assigned (1:1) to receive sibutramine 10 mg or placebo within each country.

- The dose of study drug (sibutramine or placebo) could have been increased (to 15 mg) for weight gain or inadequate weight loss at the discretion of the investigator, if well tolerated.
    - The dose of study drug then could have been subsequently decreased to 10 mg at the discretion of the investigator.

Study Management:

- Subjects were to receive continued cardioprotective diet and exercise management.
- Subjects were to receive optimum management of medical conditions (e.g., diabetes, hypertension, dyslipidemia) according to national guidelines. Of note, the investigators had no restriction placed on their selection or use of medical treatment options (other than medications contraindicated for use with sibutramine).
- Lack of weight reduction was not a criterion for discontinuation of study drug.
- If a subject experienced a CV outcome event study drug was continued at the discretion of the investigator.

Follow-up Period

During the Follow-up Period (after discontinuation of study drug), CV outcome event information was elicited by telephone every 3 months and at Annual Follow-up Visits.

5.2.2 Study Population

5.2.2.1 Key Inclusion/Exclusion Criteria

The key inclusion/enrollment criteria were the following:

- Age ≥ 55 years,
- A BMI of at least 27 kg/m^2 and no more than 45 kg/m^2, or at least 25 kg/m^2 and less than 27 kg/m^2 with a waist circumference at least 102 cm (for men)/88 cm (for women).
- One of the following (using criteria described in greater details in Table 14) for a history of:
  - Coronary artery disease (CAD),
  - Cerebrovascular disease,
  - Peripheral arterial occlusive disease (PAOD), or
  - Type 2 diabetes mellitus with at least one other cardiovascular risk factor.

The key exclusion criteria were the following:

- Recent myocardial infarction (within 3 months);
- Heart failure (> New York Heart Association [NYHA] Functional Class II);
- Significant valvulopathy or left ventricular tract obstruction;
- Constrictive pericarditis; uncorrected congenital heart disease;
- Any of the following without a pacemaker or cor pulmonale
  - Sinus bradycardia, sick sinus syndrome, or atrioventricular block (> first degree);
- SBP > 160 mmHg; DBP > 100 mmHg, pulse > 100 bpm;
- Hypertension stabilized for less than 3 months prior to enrollment;
- Syncopal episodes due to uncontrolled life-threatening arrhythmias;
- Scheduled cardiac surgery or coronary angioplasty;
- Recent (within 3 months) non-hemorrhagic stroke or transient ischemic attack (TIA); history of hemorrhagic stroke.

Table 14. Specific Criteria that Defined the Preexisting Cardiovascular Diseases

Coronary artery disease Defined as history of ≥ 1 of the following: • Previous history of a myocardial infarction, • Stable/unstable angina with documented multivessel CAD or with a positive stress test, • Multivessel percutaneous transluminal coronary angioplasty (PTCA) or stent placement, • Multivessel coronary artery bypass graft (CABG) with current angina, • Multivessel CABG ≤ 4 years prior to enrollment, and/or • Multivessel CAD with > 50% stenosis in ≥ 2 major coronary arteries seen by angiography.	**Stroke** To be non-hemorrhagic and documented by: • Computed tomography (CT) scan or magnetic resonance imaging (MRI) scan.
Peripheral arterial occlusive disease Defined as having ≥ 1 of the following: • Limb arterial bypass surgery, • Percutaneous transluminal angioplasty, • Amputation of foot or lower limb for peripheral arterial occlusive disease (PAOD), and/or • Symptoms of intermittent claudication.	**Subjects with type 2 diabetes mellitus** Must have ≥ 1 of the following CV risk factors: • Hypertension, controlled on medication with SBP ≤ 160 mmHg and DBP ≤ 90 mmHg, • Dyslipidemia, documented by total cholesterol > 5.2 mmol/L (> 200 mg/dL) and/or HDL-C < 0.9 mmol/L (< 35 mg/dL), • Current cigarette smoking, and/or • Diabetic nephropathy with evidence of microalbuminuria.

5.2.2.2 Cardiovascular (CV) Risk Groups

All subjects enrolled in SCOUT were required to be at high risk for a cardiovascular outcome event. Thus, subjects had to have known preexisting cardiovascular diseases (coronary artery disease, cerebrovascular disease, or PAOD) or Type 2 diabetes mellitus (DM) with another risk factor and had to meet strict criteria stipulated in the study protocol (Table 14). Subjects were then categorized into 1 of 3 protocol-specified CV risk groups (DM Only, CV Only, and CV + DM) (Table 15).

The CV risk groups thus classified subjects according to their potential level of CV risk; the highest-risk group was the CV + DM group, while the lowest-risk group was the DM Only group.

Table 15. Definitions of the Three CV Risk Groups

DM Only	CV Only	CV + DM
Subjects with a medical history of type 2 diabetes mellitus with at least 1 other risk factor: • Controlled hypertension (on medication) • Dyslipidemia • Current smoker • Diabetic nephropathy with microalbuminuria No medical history of preexisting cardiovascular disease according to strict criteria in study protocol.	Subjects with a medical history of cardiovascular disease according to strict criteria stipulated in study protocol: • CAD • Cerebrovascular disease • PAOD No medical history of type 2 diabetes mellitus with at least 1 other risk factor	Subjects with a medical history of cardiovascular disease according to strict criteria stipulated in study protocol: • CAD • Cerebrovascular disease • PAOD *AND* Medical history of type 2 diabetes mellitus with at least 1 other risk factor: • Controlled hypertension (on medication) • Dyslipidemia • Current smoker • Diabetic nephropathy with microalbuminuria

5.2.3 Study Endpoints

5.2.3.1 Primary and Key Secondary Endpoints

The primary endpoint analysis was the analysis of time from randomization to the first occurrence of any of the following primary outcome events (POE):

1. Nonfatal myocardial infarction
2. Nonfatal stroke
3. Resuscitated cardiac arrest (RCA)
4. Cardiovascular death (CV Death)

The key secondary endpoints were:

- Death due to any cause (All-Cause Mortality)
- POE plus revascularization procedures

  Note: Revascularization procedures of interest included PTCA, CABG, coronary artery stent placement, cardiac transplant, peripheral vascular bypass or angioplasty, and carotid endarterectomy.

5.2.4 Study Conduct

Study Sites

The SCOUT study was conducted in 16 countries in Australia, Latin America, and Europe at a total of 298 sites.

Governance Bodies

The study was overseen by an external executive steering committee (ESC) and monitored by an independent data safety monitoring board (DSMB) in accordance with standard conduct for clinical outcome studies. An independent events adjudication committee (EAC) determined the specific criteria to define the CV outcome events prior

to or shortly after study initiation, and reviewed and adjudicated the potential CV outcomes events that occurred during the study according to an event adjudication manual.

Members of these governance bodies were precluded from acting as trial investigators. The memberships and key responsibilities of each of these governance bodies are included in Appendix D. Information on the adjudication process and criteria to adjudicate outcome events is included in Appendix E.

5.2.4.1 Sample Size and Power

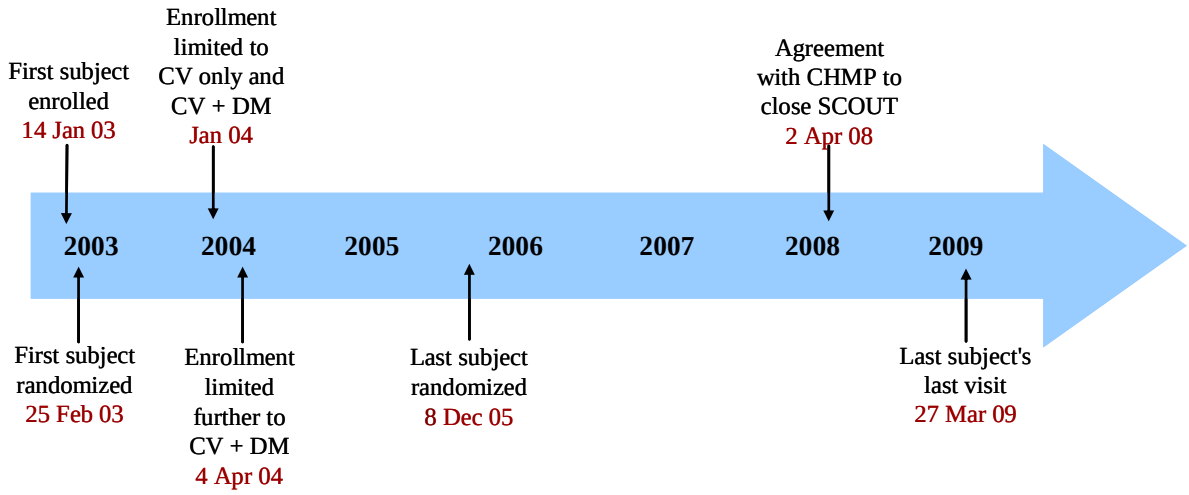
An event target of 2,160 primary outcome events (POEs) would have provided 80% power to detect an 11.4% reduction in the hazard ratio with sibutramine at the 5% level of significance using a 2-sided test.

Given the assumed placebo POE rate of 7% per year (7 events per 100 patient-years) postulated from multiple large studies that were available at the time the SCOUT study was being designed,[46–50] and assuming a 30% study drug discontinuation rate (prior to a POE in the sibutramine group) and a 2-year interval of randomization, the original sample size calculation suggested the need to randomize 9,000 subjects and follow them for a minimum of 3 years (average of 4 years) to accumulate 2,160 POEs.

5.2.5 Study Enrollment

The first subject was enrolled into SCOUT in January 2003. As early as January 2004, the ESC recognized that the overall CV event rate was lower than predicted (1.2 events per 100 patient-years compared with the anticipated overall rate of 6.5 events per 100 patient-years). Therefore, the ESC attempted to increase the CV event rate by initiating measures to increase enrollment into the higher CV risk groups (CV Only and CV + DM) by first closing enrollment into the DM Only group (January 2004), shortly thereafter closing enrollment into the CV Only group (April 2004), and subsequently only allowing enrollment into the CV + DM group.

Figure 5. Enrollment and Estimated Randomization Phase Event Rates in SCOUT



	31 Jan 04	4 Apr 04	1 Apr 05	8 Dec 05		
Subjects Enrolled	4094	5670	9084	10,777		
Estimated Event Rate (per 100 PY)	1.75	1.75	1.70	2.30	2.54	2.64
Rate as of:	9 Jan 04		9 Nov 04	1 Aug 05	15 Mar 08	27 Mar 09

As a result, the majority of SCOUT subjects met qualifications for the group with the highest cardiovascular risk, the CV + DM group (60% of the total randomized study population). Despite the restriction of enrollment to the CV + DM group, the observed SCOUT event rate remained lower than expected.

In retrospect, the observed event rate from SCOUT is similar to rates reported in more recent cardiovascular outcomes trials[51–53] and likely reflects changes in treatment options for cardiovascular risk factors available during the last decade.

5.2.6 Study Termination

During the conduct of SCOUT, the German Federal Institute for Drugs and Medical Devices (BfArM) as the reference member state (RMS) for the European approval, was informed and consulted about study matters. BfArM was provided with a series of

6-monthly updates and was informed as early as January 2004 of the lower than expected event rate.

Discussions occurred between Abbott, the ESC, and BfArM during the study regarding the option to modify the primary endpoint to add revascularization procedures to the primary composite endpoint (POE + revascularization procedures) and/or to extend the duration of the study. BfArM did not agree with these proposals and recommended that Abbott consult with the Scientific Advice Working Party (SAWP) of the CHMP to address the lower-than-expected outcome rates in the SCOUT study.

Accordingly, in December 2007, Abbott submitted a Scientific Advice Request to SAWP of the CHMP regarding SCOUT study POE rates and overall power. After a series of meetings and presentations in early 2008, the SAWP concluded that Abbott should terminate the SCOUT study in February 2009. The SAWP also determined that Abbott should not modify the primary composite endpoint, despite the low number of primary outcome events, commenting that the projected number of primary outcome events to be collected by the time of the termination of the study would be sufficient to power a non-inferiority comparison between sibutramine and placebo. The SAWP further requested that Abbott make available All-Cause Mortality data as soon as possible after the study's conclusion. The CHMP formally adopted the SAWP's scientific advice in April 2008.

In accordance with the SAWP and CHMP advice, Abbott terminated the SCOUT study short of the target number of primary outcome events. On 20 April 2009, Abbott notified regulatory agencies worldwide of the closure of SCOUT, with the last subject's last visit on 27 March 2009. The database was closed on 12 November 2009 and preliminary results became available shortly thereafter.

5.3 SCOUT Results

5.3.1 Subject Disposition

In the SCOUT study, 10,744 subjects were enrolled and treated with sibutramine in the Lead-in Period. Of these subjects, 9,996 (93%) completed the Lead-in Period and 9,805 (91.3%) were randomized. One subject enrolled in the Randomization Phase was not dispensed study drug and, therefore, was not included in the ITT population (All Subjects); the ITT population comprised 9,804 subjects: 4,898 for placebo and 4,906 for sibutramine.

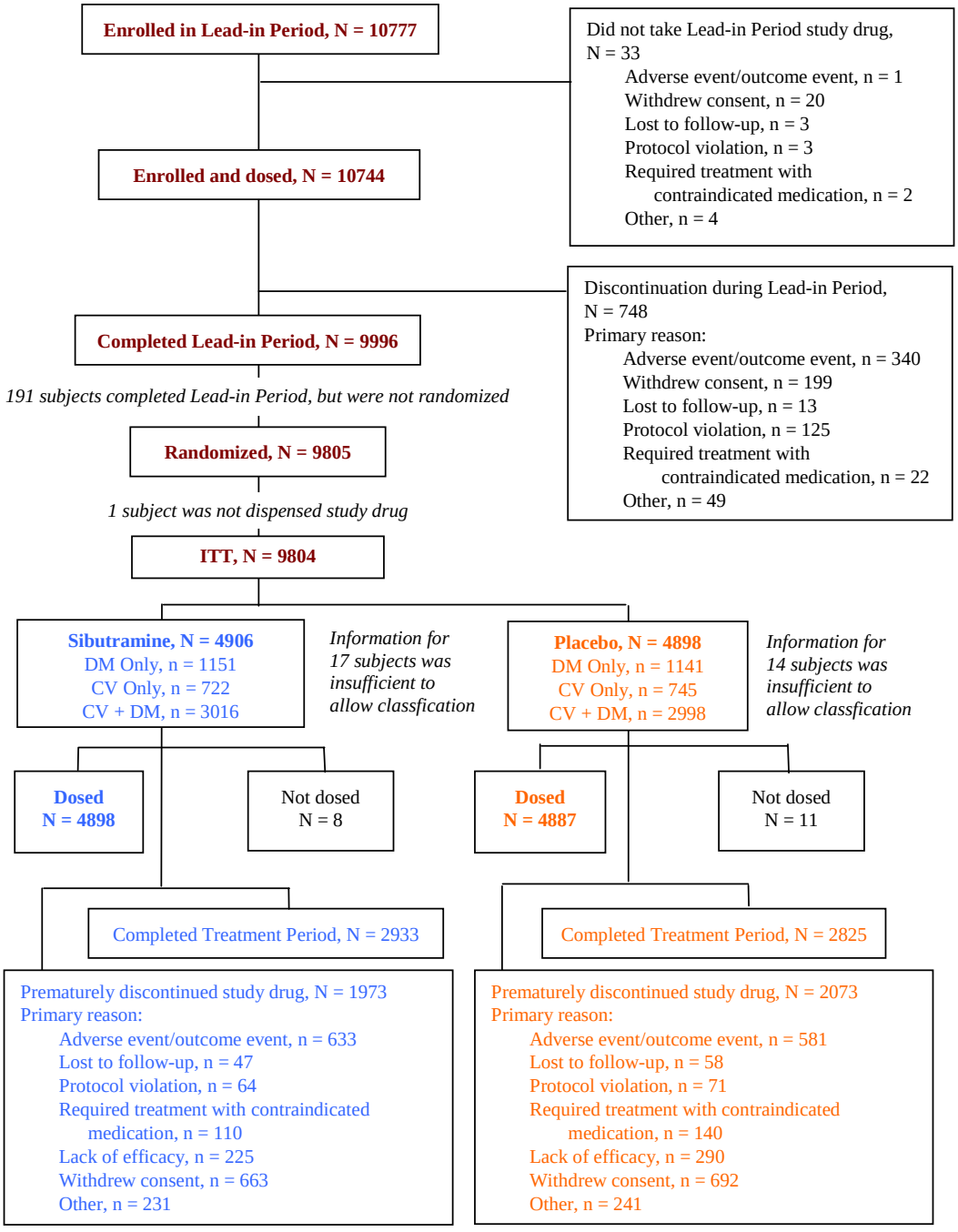
Overall mean treatment duration was 3.4 years (interquartile range 2.1 to 4.7 years) during which 2,073 placebo-treated subjects (42.3%) and 1,973 sibutramine-treated subjects (40.2%) permanently discontinued study drug (mean treatment duration: 3.3 years for placebo-treated subjects; 3.4 years for sibutramine-treated subjects).

Outcome event status was obtained on the majority of study subjects including those who prematurely discontinued from the study procedures. Final outcome event status for nonfatal events was unknown for 4% of subjects (N = 397; placebo n = 202 and sibutramine n = 195) and survival status was unknown for 1% of subjects (N = 95; placebo n = 40 and sibutramine n = 55).

Total study duration for evaluation of the POE was 41,408 person-years: 20,626 person-years for sibutramine and 20,782 person-years for placebo and for evaluation of All-Cause Mortality, it was 42,706 person-years: 21,360 person-years for sibutramine and 21,346 person-years for placebo.

Disposition of the ITT population is presented in Figure 6.

Figure 6. Disposition of Subjects: ITT Population



A total of 1,308 sibutramine-treated subjects (26.7% of all sibutramine-treated subjects) permanently titrated to 15 mg sibutramine. This represents 81.1% of the subjects who ever received 15 mg sibutramine (1,308/1,613).

5.3.2 Baseline Demographics

Summaries of demographics and baseline characteristics for the ITT population are presented for all subjects and by treatment group.

In the ITT population, subjects in the 2 treatment groups were generally similar with respect to Lead-in Period baseline demographics and other characteristics (Table 16 and Table 17).

Table 16. Demographics at Lead-in Period Baseline for the ITT Population

	Number (%)		
Variable	**Placebo N = 4898**	**Sibutramine N = 4906**	**Total N = 9804**
Gender, n (%) male	2843 (58.0)	2807 (57.2)	5650 (57.6)
Race, n (%) white	4722 (96.4)	4733 (96.5)	9455 (96.5)
Hispanic ethnicity, n (%)	131 (2.7)	134 (2.7)	265 (2.7)
Age, yrs			
Mean (SD)	63.3 (6.15)	63.2 (6.09)	63.2 (6.12)
≥ 65, n (%)	1901 (38.8)	1866 (38.0)	3767 (38.4)
Geographic region, n (%)			
Europe	4150 (84.7)	4160 (84.8)	8310 (84.8)
Central and South America	363 (7.4)	362 (7.4)	725 (7.4)
Australia	385 (7.9)	384 (7.8)	769 (7.8)
Body weight, kg			
Mean (SD)	96.21 (15.491)	96.27 (15.433)	96.24 (15.462)
BMI, kg/m^2			
Mean (SD)	34.40 (4.505)	34.50 (4.572)	34.45 (4.539)
SBP, mmHg			
Mean (SD)	138.20 (12.617)	138.21 (12.870)	138.21 (12.743)
DBP, mmHg			
Mean (SD)	77.88 (8.367)	77.82 (8.406)	77.85 (8.386)
Pulse, bpm			
Mean (SD)	71.15 (10.066)	71.14 (10.232)	71.14 (10.149)
Rate-pressure product,			
Mean (SD)	98.46 (17.380)	98.46 (17.727)	98.46 (17.554)

Rate-pressure product = SBP mmHg•pulse bpm/100

Table 17. Disease Characteristics at Lead-in Period Baseline for the ITT Population

Variable	Number (%)		
	Placebo N = 4898	Sibutramine N = 4906	Total N = 9804
CV risk group			
DM Only	1141 (23.4)	1151 (23.5)	2292 (23.5)
CV Only	745 (15.3)	722 (14.8)	1467 (15.0)
CV + DM	2998 (61.4)	3016 (61.7)	6014 (61.5)
Unknown	14	17	31
History of DM at Screening			
Yes	4125 (84.2)	4154 (84.7)	8279 (84.4)

Summaries of demographics and baseline characteristics for the CV risk groups are presented in Table 18. Subjects in the 2 treatment groups were generally similar in each of the 3 CV risk groups with respect to Lead-in Period baseline demographics and other characteristics. However, the characteristics of the DM Only group differed from those of the CV Only and CV + DM groups (e.g., greater proportion of women and younger mean age in the DM Only group).

Table 18. Demographics at Lead-in Period Baseline for the CV Risk Groups

	Number (%)					
	DM Only N = 2292		CV Only N = 1467		CV + DM N = 6014	
Variable	**PBO N = 1141**	**SBT N = 1151**	**PBO N = 745**	**SBT N = 722**	**PBO N = 2998**	**SBT N = 3016**
Gender, n (%) male	428 (37.5)	432 (37.5)	505 (67.8)	448 (62.0)	1903 (63.5)	1920 (63.7)
Age, yrs						
Mean (SD)	62.0 (5.53)	61.6 (5.37)	63.1 (6.15)	63.4 (5.94)	63.8 (6.30)	63.7 (6.28)
≥ 65, n (%)	345 (30.2)	316 (27.5)	280 (37.6)	285 (39.5)	1273 (42.5)	1259 (41.7)
Body weight, kg						
Mean (SD)	97.18 (15.81)	98.18 (16.48)	95.05 (15.21)	94.19 (14.59)	96.11 (15.43)	96.04 (15.14)
SBP, mmHg						
Mean (SD)	140.42 (12.228)	140.88 (12.319)	136.15 (13.102)	135.98 (13.050)	137.85 (12.527)	137.73 (12.880)
DBP, mmHg						
Mean (SD)	78.17 (8.283)	78.64 (8.221)	78.62 (8.522)	78.17 (8.499)	77.58 (8.356)	77.42 (8.434)
Pulse, bpm						
Mean (SD)	74.31 (10.213)	74.52 (10.347)	67.89 (9.456)	67.95 (9.704)	70.76 (9.826)	70.60 (9.965)
Rate-pressure product						
Mean (SD)	104.50 (17.889)	105.04 (17.685)	92.53 (16.307)	92.59 (17.023)	97.64 (16.766)	97.35 (17.172)

PBO = placebo; SBT = sibutramine

Rate-pressure product = SBP mmHg•pulse bpm/100

At Lead-in Period baseline, concomitant medication usage, similar for both treatment groups, was as follows for all subjects:

- 61% of subjects were treated with a beta-blocker.
- 78% of subjects were treated with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), and/or spironolactone.
- 79% of subjects were treated with aspirin, an anticoagulant, and/or an antiplatelet agent.

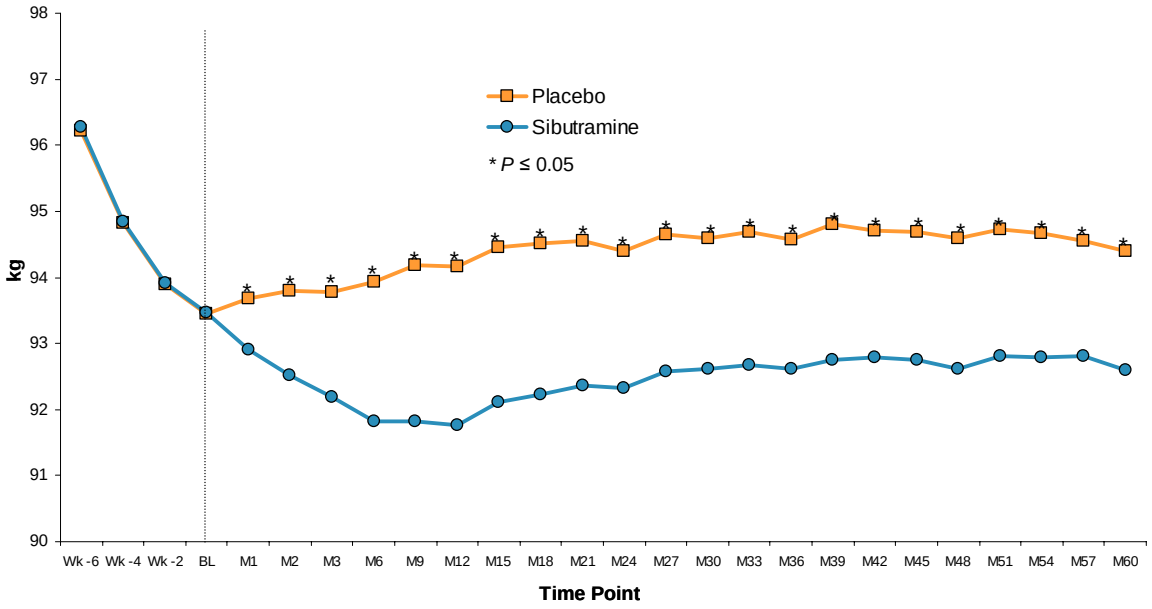
- 67% of subjects were treated with statins.
- 26% of subjects were treated with insulin.
- 59% of subjects were treated with a biguanide (metformin), sulfonylurea, thiazolidinedione (TZD), and/or meglitinide.

5.3.3 Weight Loss Results

The SCOUT study confirmed that sibutramine is an effective treatment for weight loss and weight loss maintenance.

During the 6-week Lead-in Period, during which all subjects received 10 mg of sibutramine, the mean reduction in body weight observed over the 6-week period was –2.56 kg (or –2.75%) for those subjects who continued into the Randomization Phase. Overall, the sibutramine group achieved and maintained greater weight loss compared with the placebo group; the difference ranged from 0.81 to 2.43 kg during the Treatment Period. Both treatment groups showed limited mean weight regain during the Treatment Period (Figure 7).

Figure 7. Mean Body Weight from Lead-in Period Baseline to Month 60: ITT Population



Number of Observations	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Sibutramine	4905	4214	3713	3345	2315	1023
Placebo	4897	4105	3570	3191	2252	961

Mean, absolute and percent change in body weight from Lead-in Period Baseline at Months 3, 6 and 12 were greater in the sibutramine treatment group than the placebo treatment group (Table 19).

Table 19. Changes in Body Weight from Lead-in Period Baseline: ITT Population

	Month 3		Month 6		Month 12	
	PBO	SBT	PBO	SBT	PBO	SBT
Mean change (kg)	–2.24	–3.83	–2.08	–4.19	–1.86	–4.27
Mean % change	–2.41	–4.08	–2.25	–4.48	–2.01	–4.55
≥ 5% responders	19.5%	30.4%	18.1%	36.5%	17.8%	36.4%

PBO = placebo; SBT = sibutramine

Note: Responders lost 5% of body weight from Lead-in Period Baseline at the month specified.

Of note, 30.4% of the sibutramine-treated subjects lost at least 5% of their body weight after approximately 3 months of treatment. This finding is quite remarkable since SCOUT included an elderly (38.4% of those randomized were ≥ 65 years of age) and primarily diabetic population (84.4%) who are known to be highly resistant to weight loss interventions. In fact, many diabetic patients gain weight as a result of their concomitant anti-diabetic medication.[38]

In comparison, 19.5% of the placebo-treated subjects lost at least 5% of their body weight after approximately 3 months of the study. Importantly, 53.0% of those placebo-treated subjects had achieved at least 5% weight loss during the Lead-in Period (when all subjects received sibutramine). Therefore, the weight loss reported for the placebo group was probably due, in large part, to treatment with sibutramine during the Lead-in Period.

5.3.4 Obesity Comorbidities Results

Investigators in SCOUT were required to optimally manage their subject's medical conditions according to local treatment guidelines. Therefore, it is not possible to determine whether changes noted in the lipid and glycemic variables were as a result of weight loss, sibutramine therapy, changes in concomitant medications, or a combination thereof.

At Lead-in Baseline, concomitant medication usage (by class) was similar in both treatment groups (Table 20). At final visit, review of the concomitant medication classes

showed that there was a similar pattern during the Treatment Period in the percentage of subjects in both treatment groups taking concomitant statins, fibrates, insulin, and other diabetic medication.

Table 20. Changes in Concomitant Medication Class from Lead-in Period Baseline to Final Visit of the Treatment Period

	Percentage of Subjects Who Reported Medication Use	
Medications	**Placebo (N = 4898) n (%)**	**Sibutramine (N=4906) n (%)**
Statin		
Lead-in baseline	3235 (66.0)	3288 (67.0)
Final visit	3902 (79.7)	3966 (80.8)
Fibrates		
Lead-in baseline	466 (9.5)	492 (10.0)
Final visit	660 (13.5)	675 (13.8)
Insulin		
Lead-in baseline	1227 (25.1)	1250 (25.5)
Final visit	1648 (33.6)	1644 (33.5)
Biguanide (metformin), sulfonylurea, TZD, and/or meglitinide		
Lead-in baseline	2856 (58.3)	2888 (58.9)
Final visit	3294 (67.3)	3337 (68.0)

Also at Month 60, there was no clinically meaningful difference between the treatment groups for changes in glycosylated hemoglobin (HbA_{1c}), total cholesterol, HDL-C, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), triglycerides, total bilirubin, or uric acid (Table 21).

Table 21. Mean Percent Change in Metabolic Variables from Lead-in Baseline to Month 60: ITT Population, MMRM Analysis

	Mean % Change[a] to Month 60				
	Placebo		Sibutramine		
Variable	N		N		Treatment Difference
HbA_{1c}[b]	850	0.26	936	0.48	0.22***
Total cholesterol	1372	–8.08	1458	–6.26	1.82**
LDL-C	1370	–10.26	1457	–7.95	2.31*
HDL-C	1372	3.61	1458	5.07	1.46**
VLDL-C	1296	–0.71	1375	–0.98	–0.28
Triglycerides	1372	–0.13	1458	0.67	0.80
Total bilirubin	1372	8.63	1458	4.44	–4.19***
Uric acid	1371	9.57	1458	8.08	–1.49*

a. For HbA_{1c} mean changes rather than mean percent changes are shown.

b. Only determined in subjects with diabetes at Lead-in Period baseline.

*,**,*** Statistically significant at the 0.05, 0.01, and 0.001 level of significance, respectively.

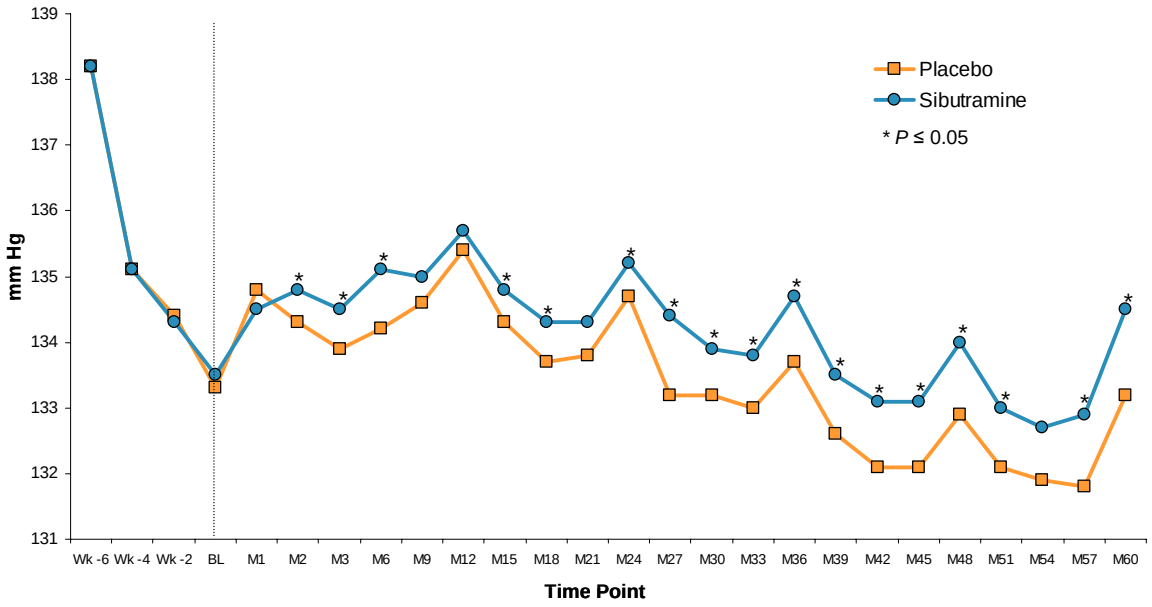
5.3.5 Vital Signs Results

5.3.5.1 Mean Changes Over Time

Sibutramine's effect on blood pressure and pulse, as observed in SCOUT, was similar to findings observed in the registration studies. The schedule for collection of vital signs information in SCOUT was typical for an outcome study but not as extensive as that undertaken in the sibutramine registration program where the effects of sibutramine on blood pressure and pulse were well defined. In SCOUT, more frequent collection of vital signs occurred during the first 4 to 5 months of the study but, thereafter, was limited to quarterly or annual study visits.

Mean SBP remained below initial values in both groups throughout the Treatment Period but was consistently higher in the sibutramine group compared with the placebo group; the differences in mean SBP ranged from –0.4 to 1.1 mmHg (Figure 8).

Figure 8. Mean Systolic Blood Pressure from Lead-in Period Baseline to Month 60: ITT Population



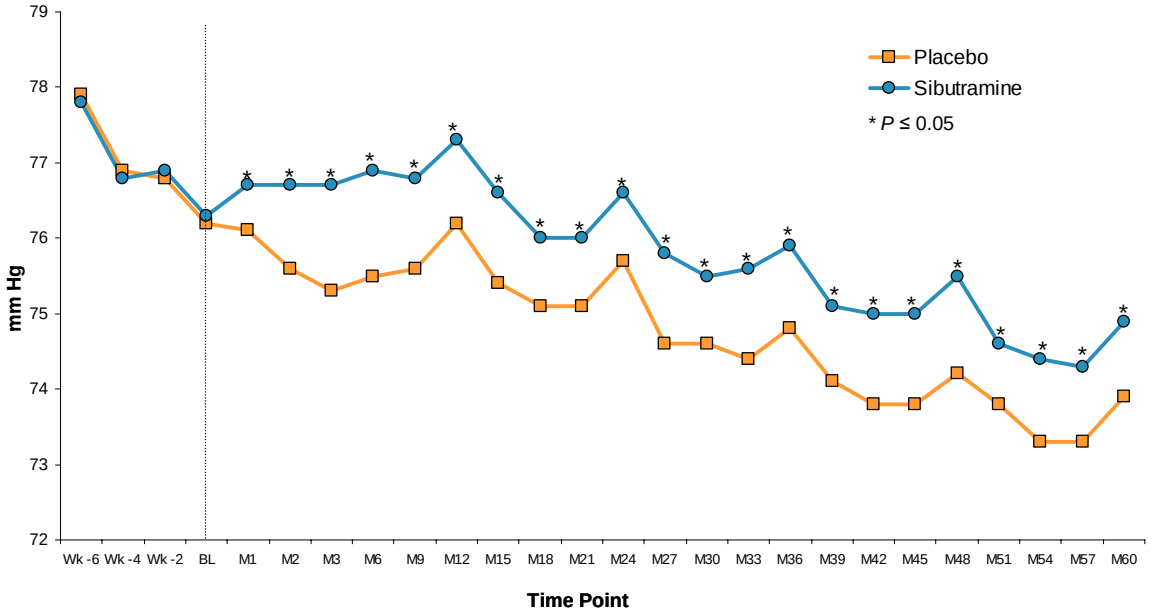
Number of Observations	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Sibutramine	4905	4215	3712	3344	2318	1023
Placebo	4897	4104	3571	3193	2250	960

Wk = Week; BL = Baseline, M = Month

During the Treatment Period, the overall difference between treatment groups for mean changes in SBP over time was statistically significant according to the MMRM analysis ($P < 0.001$).

Likewise, mean DBP remained below initial values in both groups throughout the Treatment Period but was consistently higher in the sibutramine group compared with the placebo group; the differences in mean DBP ranged from 0.6 to 1.4 mmHg (Figure 9).

Figure 9. Mean Diastolic Blood Pressure from Lead-in Period Baseline to Month 60: ITT Population, Observed Cases



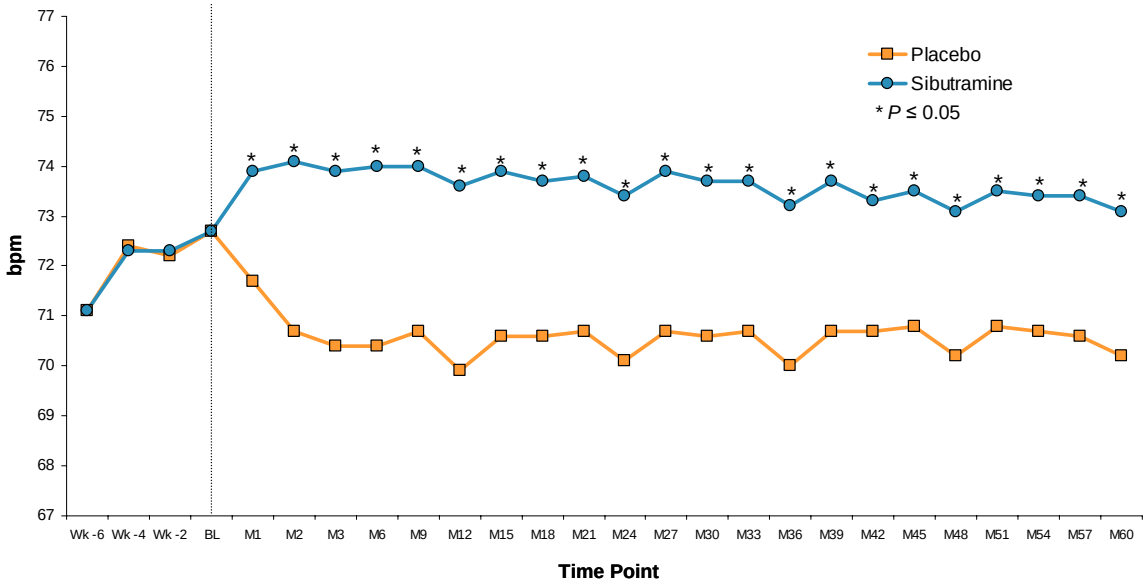
Number of Observations	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Sibutramine	4905	4215	3712	3344	2318	1023
Placebo	4897	4104	3571	3193	2250	960

Wk = Week; BL = Baseline, M = Month

During the Treatment Period, the overall difference between treatment groups for mean changes in DBP over time was statistically significant at each time point.

Mean pulse remained consistently higher during the Treatment Period in the sibutramine group compared with the placebo group; the differences in mean pulse ranged from 2.2 to 3.7 bpm (Figure 10).

Figure 10. Mean Pulse from Lead-in Period Baseline to Month 60: ITT Population



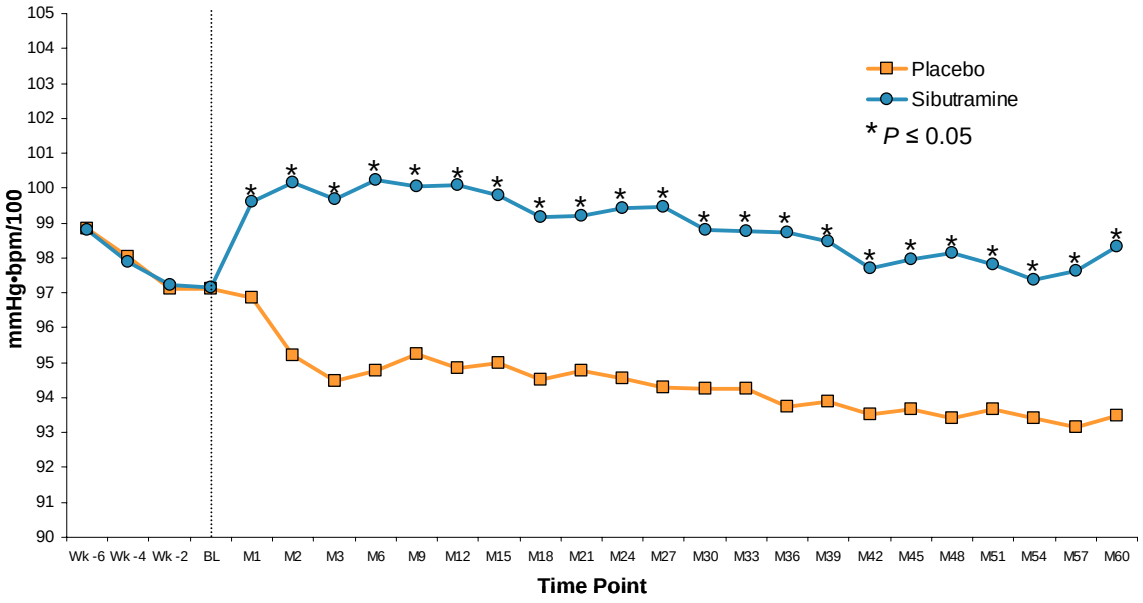
Number of Observations	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Sibutramine	4904	4211	3713	3342	2316	1023
Placebo	4896	4101	3570	3190	2251	958

Wk = Week; BL = Baseline, M = Month

During the Treatment Period, the overall difference between treatment groups for mean changes in pulse was statistically significant according to the MMRM analysis ($P < 0.001$).

Mean rate-pressure product (SBP•pulse/100) was consistently higher in the sibutramine group compared with the placebo group during the Treatment Period; differences in mean rate-pressure product ranged from 2.8 to 5.5 mmHg•bpm/100 (Figure 11).

Figure 11. Mean Systolic Blood Pressure * Pulse Product from Lead-in Period Baseline to Month 60: ITT Population



Number of Observations	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Sibutramine	4904	4211	3710	3341	2316	1023
Placebo	4896	4101	3570	3189	2249	958

Wk = Week; BL = Baseline; M = Month

During the Treatment Period, the overall difference between treatment groups for mean changes in systolic blood pressure–heart rate product was statistically significant according to the MMRM analysis ($P < 0.001$).

The relationships between changes in blood pressure or pulse and weight loss were evaluated for subjects with at least 5%, at least 10%, or at least 15% weight loss through the end of the Treatment Period. The results are presented in Figure 12 through Figure 14.

The mean reduction of SBP and DBP was proportional to the degree of weight loss, but was greater in the placebo group as compared to the sibutramine group. Pulse remained higher in the sibutramine group, and was consistent regardless of weight loss.

Figure 12. Mean Systolic Blood Pressure for Weight-loss Categories from Lead-in Period Baseline to Month 60: ITT Population, LOCF

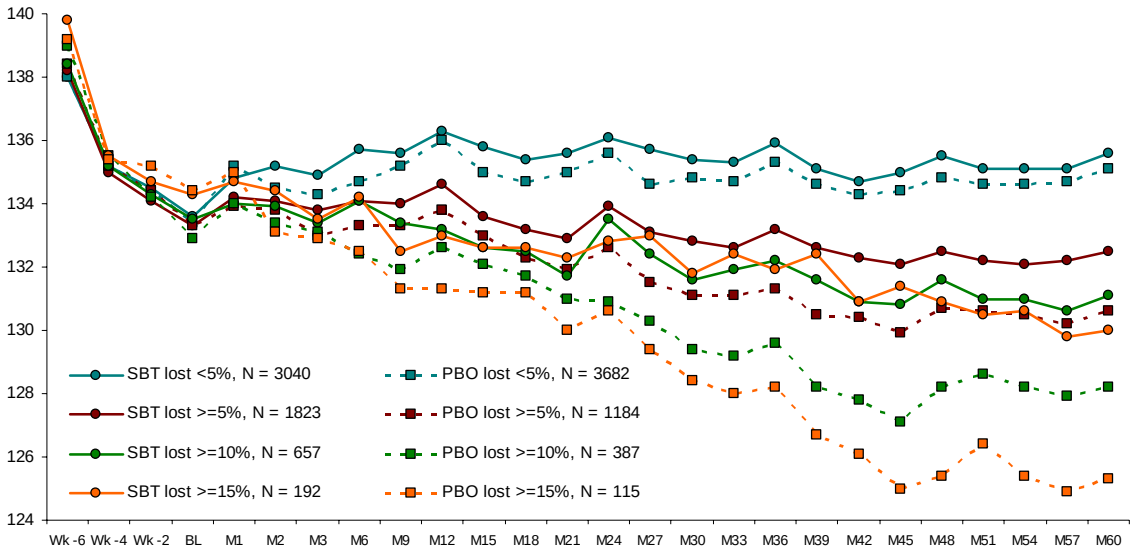


Figure 13. Mean Diastolic Blood Pressure for Weight-loss Categories from Lead-in Period Baseline to Month 60: ITT Population, LOCF

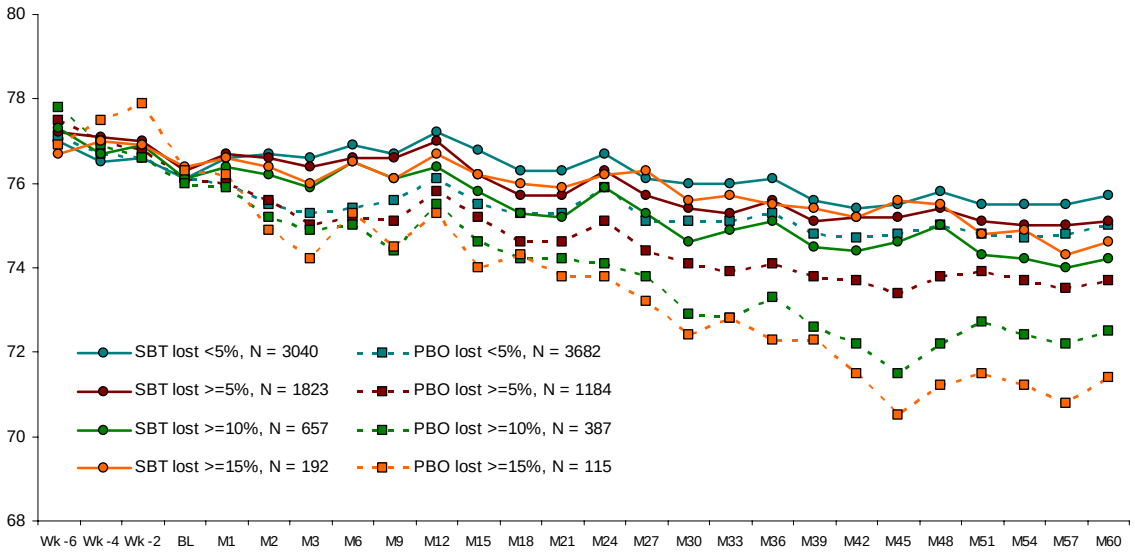
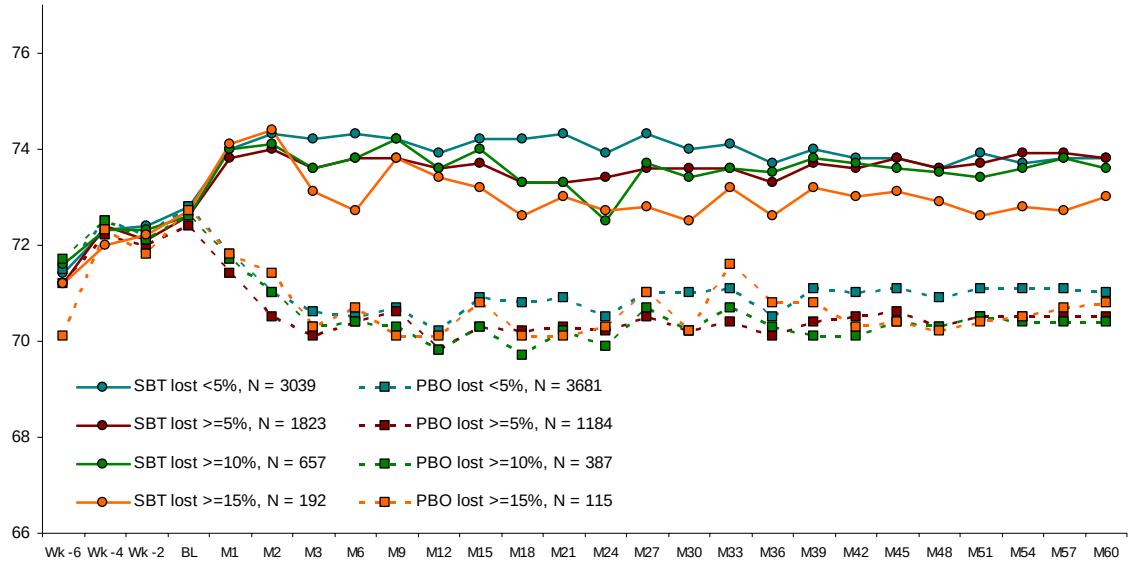


Figure 14. Mean Pulse for Weight-loss Categories from Lead-in Period Baseline to Month 60: ITT Population, LOCF



5.3.5.2 Vital Sign Outlier Assessment

Evaluations were performed to identify subjects with potentially clinically significant increases above baseline in SBP or DBP (≥ 10 mmHg) or pulse (≥ 10 bpm) at 2 consecutive study visits during the first 3 months of treatment (Table 22). A higher percentage of subjects in the sibutramine group had increases as compared to the placebo group.

Table 22. Summary of Subjects with 2 Consecutive Increases in Blood Pressure or Pulse: LOCF

	n/N (%)	
Time Point	**Placebo**	**Sibutramine**
Month 3 from Lead-in Period Baseline	1034/4897 (21.1)	1349/4905 (27.5)

Note: From Lead-in Period Baseline through combined Lead-in and Treatment Period.

5.3.5.3 Antihypertensive Medication Use

In SCOUT, a low percentage (12.1% for sibutramine and 12.0% for placebo) of subjects were not taking antihypertensive medication at baseline. Of these subjects, a higher percentage of subjects in the sibutramine group initiated antihypertensive therapy during the study (Table 23).

Table 23. Number of Subjects Not Taking any Antihypertensive at Baseline Who Were Taking Antihypertensives at Final Visit

	n/N (%)	
Antihypertensive Use	**Placebo**	**Sibutramine**
No medication at Baseline	546/4537 (12.0%)	557/4603 (12.1%)
On medication at Final Visit	134/546 (24.5%)	176/557 (31.6%)

Note: Only subjects with both a baseline and at least 1 postbaseline visit were included in the summary.

For subjects taking an antihypertensive medication at baseline, generally similar increases in the number of classes used and similar increases of use by class were observed between the treatment groups (Table 24).

Table 24. Number of Subjects Taking Antihypertensive Medications at Baseline and at Final Visit by Number of Classes and by Class Name

Number of Classes of Antihypertensive Medication Taken	Number (%)			
	Medication Use at Baseline		Medication Use at Final Visit	
	Placebo	Sibutramine	Placebo	Sibutramine
None	596 (12.2)	598 (12.2)	492 (10.0)	455 (9.3)
1	945 (19.3)	1002 (20.4)	716 (14.6)	746 (15.2)
2	1473 (30.1)	1391 (28.4)	1244 (25.4)	1229 (25.1)
3	1246 (25.4)	1267 (25.9)	1277 (26.1)	1326 (27.0)
4	541 (11.0)	559 (11.4)	648 (13.2)	683 (13.9)
5	96 (2.0)	88 (1.8)	160 (3.3)	164 (3.3)
Medication Class	**n/N (%)**			
Beta-blocker	2476/4897 (50.6)	2427/4905 (49.5)	2418/4537 (53.3)	2547/4603 (55.3)
Diuretic	2192/4897 (44.8)	2161/4905 (44.1)	2343/4537 (51.6)	2355/4603 (51.2)
ACE inhibitor/ARB	3522/4897 (71.9)	3549/4905 (72.4)	3479/4537 (76.7)	3561/4603 (77.4)
Calcium channel blocker	1639/4897 (33.5)	1673/4905 (34.1)	1638/4537 (36.1)	1705/4603 (37.0)
Other	444/4897 (9.1)	451/4905 (9.2)	549/4537 (12.1)	566/4603 (12.3)

5.3.5.4 Adverse Events of Interest by Standardized MedDRA Queries (SMQ)

Aside from cardiovascular outcomes, an assessment of SCOUT for psychiatric adverse events was conducted. Serious adverse events of special interest were defined by the following SMQs:

- Suicide/self-injury
- Drug abuse
- Depression (excluding suicide and self injury)
- Psychosis and psychotic disorders

Serious adverse events for these SMQs occurred in < 0.1% of subjects in both treatment groups with the exception of the Depression SMQ, with an incidence of 0.2% in the placebo group and < 0.1% in the sibutramine group.

No statistically significant difference between treatment groups was seen for any SMQ. There was no reported event in the Drug Abuse SMQ. Importantly, less than 0.1% of subjects in either treatment group reported serious adverse events in the Suicide/ Self-Injury SMQ or the Psychosis and Psychotic Disorders SMQ. Serious adverse events for preferred terms within these SMQs that were reported during the Randomization Phase and occurred with a difference between groups of at least 0.1% are shown in Table 25.

Table 25. SMQs for Treatment-Emergent Serious Adverse Events of Special Interest During the Randomization Phase: Randomization Phase Safety Population

	Number (%) of Subjects	
SMQ	**Placebo N = 4881**	**Sibutramine N = 4904**
Depression (excluding suicide and self-injury)	10 (0.2)	3 (< 0.1)
Depression (preferred term)	10 (0.2)	3 (<0.1)
Suicide/self-injury	2 (< 0.1)	1 (< 0.1)
Psychosis and psychotic disorders	3 (< 0.1)	4 (< 0.1)
Drug abuse	0	0

5.4 Results for Cardiovascular Outcomes and Death

5.4.1 Primary Endpoint

The primary endpoint analysis for SCOUT was the time-to-event analysis of the first occurrence of a primary outcome event (POE). POE included nonfatal MI, nonfatal stroke, resuscitated cardiac arrest (RCA), and CV Death.

All POE met prespecified criteria (per Appendix E) as assessed by the SCOUT Events Adjudication Committee (EAC). Final outcome event status is unknown for 4.0% of subjects and survival status is unknown for 1.0% of subjects.

The primary endpoint result showed a 16% increased risk for POE in the sibutramine group relative to the placebo group (Table 26).

Table 26. Primary Endpoint: ITT Population

	Placebo	Sibutramine	HR[a]	95% CI	*P* value[b]
Primary outcome event	490 (10.0%)	561 (11.4%)	1.162	1.029, 1.311	0.015
Event rate per 100 person-years	2.36	2.72			

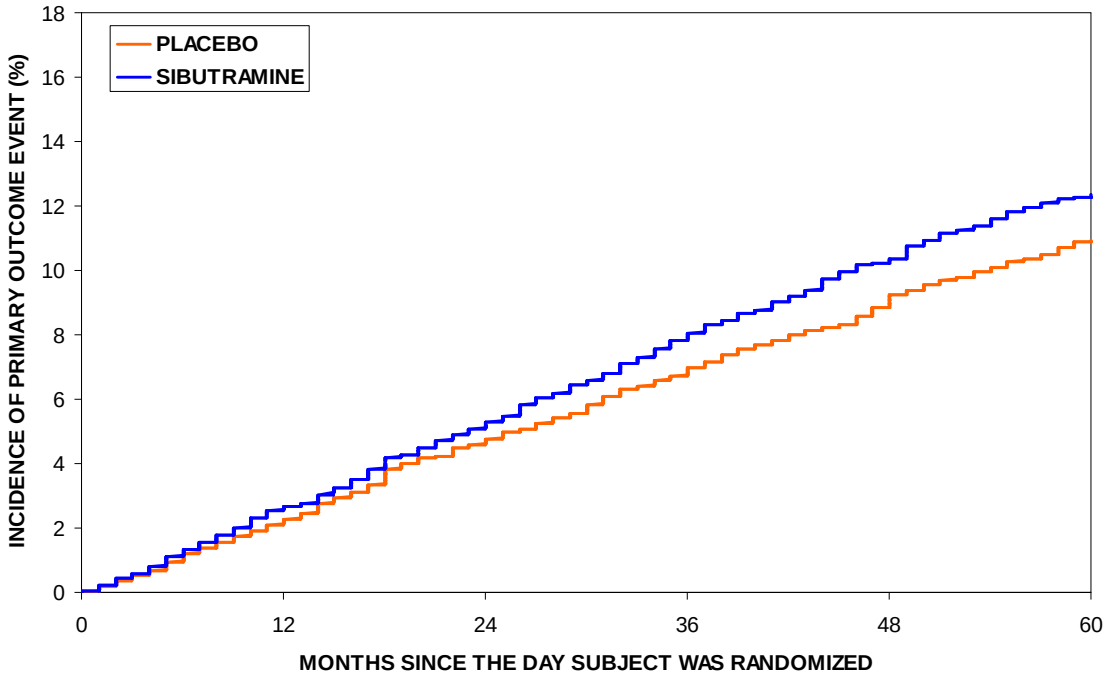
a. The HR is for treatment effect.

b. The *P* value is from a Cox proportional hazards model adjusted for country, gender, and age at Lead-in Period Baseline.

Note: Event rate per 100 person-years is based on the first event, and the time to that event, for each subject. For subjects without events, their full follow-up time was included

The primary endpoint result, depicted by Kaplan-Meier (KM) curves (Figure 15), demonstrates that the event rate was fairly constant over time in both treatment groups. The event rate was 2.36 per 100 person-years for the placebo group and 2.72 per 100 person-years for the sibutramine group.

Figure 15. Kaplan-Meier Curves of the Primary Endpoint: ITT Population



Subjects at risk

Placebo	4898	4776	4623	4482	3467	1730
Sibutramine	4906	4749	4601	4427	3403	1720

Note: Plot has been truncated at Month 60 for graphical purposes. All data were included in the analysis.

5.4.1.1 Sensitivity Analyses for the Primary Endpoint

The protocol definition of POE included all confirmed events following randomization through the study's last patient's last visit (LPLV), regardless of whether the subject was on study drug. Two sensitivity analyses with alternative definitions for the POE timeframe were conducted to better understand the occurrence of the POE in relationship to study drug administration.

- POE restricted to events that occurred on study drug (during the Treatment Period)
- POE including any additional events that may have occurred after the study's LPLV date (27 March 2009)

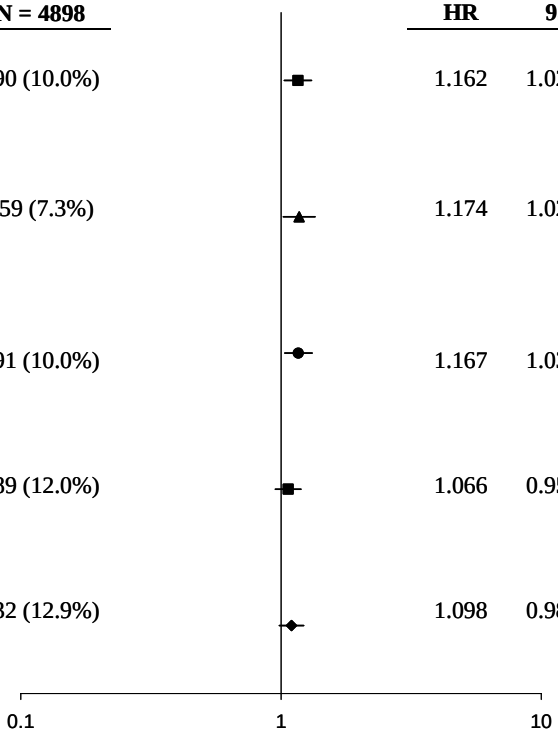
Adjudication procedures included event definitions and objective criteria to ensure consistency in the evaluation of outcome events. As the threshold for adjudication required confirmatory data, there may have been some investigator-reported adverse events that were cardiovascular in origin but did not have the necessary information to confirm a POE. To address this issue, 2 sensitivity analyses using all investigator-reported adverse events were conducted. (See Appendix F for details.)

- Adverse events potentially representing POE, regardless of whether the adjudication criteria were met (including only adverse events) were analyzed. Only the first occurrence of an adverse event for each subject is included in the time-to-event analysis.
- The combination of adverse events potentially representing POE and confirmed POEs by adjudication was analyzed. Only the first occurrence of an adverse event or POE for each subject is included in the time-to-event analysis.

The results from these sensitivity analyses are consistent with results of the primary endpoint (Figure 16).

Figure 16. Sensitivity Analyses of the Primary Endpoint: ITT Population

Analysis	Number (%) with endpoint: Sibutramine N = 4906	Number (%) with endpoint: Placebo N = 4898	HR	95% CI	*P* value
POE	561 (11.4%)	490 (10.0%)	1.162	1.029, 1.311	0.015
Including only POE during Treatment Period	426 (8.7%)	359 (7.3%)	1.174	1.020, 1.351	0.025
Including all POE after LPLV	565 (11.5%)	491 (10.0%)	1.167	1.034, 1.317	0.012
Including only adverse events	622 (12.7%)	589 (12.0%)	1.066	0.952, 1.193	0.268
Including adverse events and adjudicated POE	685 (14.0%)	632 (12.9%)	1.098	0.985, 1.223	0.090



5.4.1.2 Primary Outcome Events Plus Revascularization Procedures

Information was collected regarding revascularization procedures of interest performed during the study (Randomization Phase). The incidence of these revascularization procedures was similar between the treatment groups (Table 27).

Table 27. Summary of Revascularization Procedures During the Randomization Phase: ITT Population

	Number (%)	
Outcome Event	**Placebo N = 4898**	**Sibutramine N = 4906**
Revascularization procedures		
Percutaneous transluminal coronary angioplasty	189 (3.9)	208 (4.2)
Coronary artery bypass grafting	78 (1.6)	90 (1.8)
Coronary artery stent placement	190 (3.9)	216 (4.4)
Cardiac transplant	2 (< 0.1)	0
Peripheral vascular bypass	24 (0.5)	44 (0.9)
Peripheral angioplasty	80 (1.6)	74 (1.5)
Carotid endarterectomy	20 (0.4)	19 (0.4)

A time-to-event analysis was used to evaluate the risk of a composite outcome of either a POE or revascularization procedure. This analysis showed a 9.7% increased risk for these events in the sibutramine group relative to the placebo group (Table 28). This finding is consistent with the results for the primary endpoint.

The event rate for this combined POE or revascularization procedure endpoint was 5.94 per 100 person-years for the placebo group and 6.38 per 100 person-years for the sibutramine group.

Table 28. Number (%) of Subjects Experiencing POE or Revascularization Procedures: ITT Population

	Placebo	**Sibutramine**	**HR[a]**	**95% CI**	***P* value[b]**
POE + revascularization procedures	856 (17.5%)	927 (18.9%)	1.097	0.999, 1.204	0.051
Event rate per 100 person-years	5.94	6.38			

a. The HR is for treatment effect.

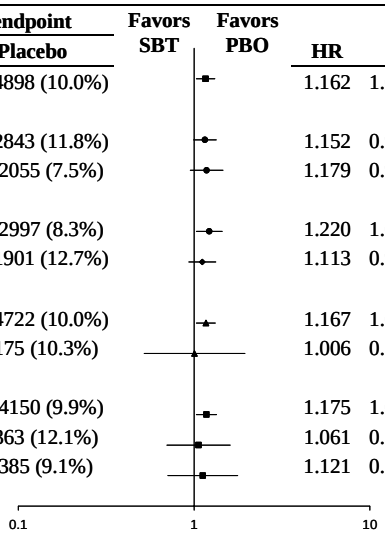
b. The *P* value is from a Cox proportional hazards model adjusted for country, gender, and age at Lead-in Period Baseline.

5.4.1.3 Subgroup Analyses for the Primary Endpoint

Additional time-to-event analyses evaluated risk of a POE within subgroups defined by gender, age, race, or geographic region of study conduct. No clinically relevant differences were noted for any of these subgroups (Figure 17).

Figure 17. Primary Endpoint Results in Subgroups: ITT Population

Analysis	Number (%) with endpoint Sibutramine	Placebo	HR	95% CI	*P* value	Interaction *P* value
ITT	561/4906 (11.4%)	490/4898 (10.0%)	1.162	1.029, 1.311	0.015	NA
Gender						
Male	376/2807 (13.4%)	335/2843 (11.8%)	1.152	0.994, 1.335	0.060	0.874
Female	185/2099 (8.8%)	155/2055 (7.5%)	1.179	0.952, 1.459	0.132	
Age						
< 65 years	301/3040 (9.9%)	249/2997 (8.3%)	1.220	1.031, 1.443	0.021	0.460
≥ 65 years	260/1866 (13.9%)	241/1901 (12.7%)	1.113	0.933, 1.326	0.234	
Race						
Caucasian	543/4733 (11.5%)	472/4722 (10.0%)	1.167	1.032, 1.320	0.014	0.675
Non-Caucasian	18/172 (10.5%)	18/175 (10.3%)	1.006	0.520, 1.946	0.986	
Geographic region						
Europe	476/4160 (11.4%)	411/4150 (9.9%)	1.175	1.030, 1.341	0.017	0.885
Central/South America	46/362 (12.7%)	44/363 (12.1%)	1.061	0.701, 1.605	0.780	
Australia	39/384 (10.2%)	35/385 (9.1%)	1.121	0.710, 1.770	0.623	



SBT = sibutramine; PBO = placebo

The age range for the ITT population was 51 to 88 years.

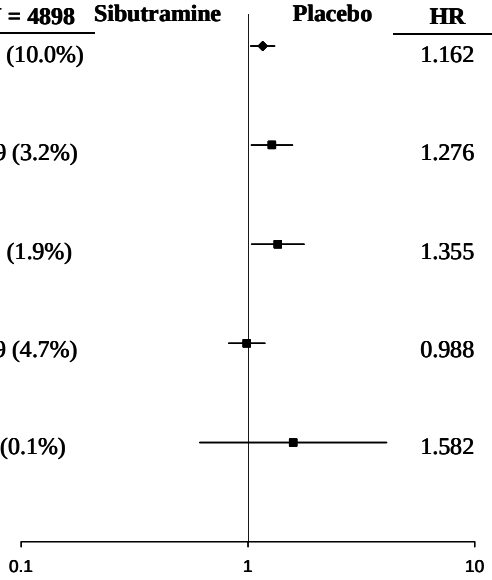
Interaction *P* values were not significant for any subgroup.

5.4.1.4 Analyses of the Individual Outcome Events for the Primary Endpoint

Analysis of the individual components of the POE showed that the increased risk in the sibutramine group was due to nonfatal MI and nonfatal stroke events. There was no apparent difference in risk for CV Deaths. Resuscitated cardiac arrest (RCA) occurred in ≤ 0.2% of subjects in either treatment group (Figure 18) and, therefore, will not be discussed further.

Figure 18. Individual Cardiovascular Outcome Events Included in the Primary Endpoint: ITT Population

Analysis	Number (%) with endpoint: Sibutramine N = 4906	Placebo N = 4898	HR	95% CI	*P*value
POE	561 (11.4%)	490 (10.0%)	1.162	1.029, 1.311	0.015
Nonfatal MI	200 (4.1%)	159 (3.2%)	1.276	1.036, 1.571	0.022
Nonfatal stroke	127 (2.6%)	95 (1.9%)	1.355	1.038, 1.767	0.025
CV death	223 (4.5%)	229 (4.7%)	0.988	0.822, 1.188	0.899
RCA	11 (0.2%)	7 (0.1%)	1.582	0.613, 4.081	0.343



5.4.2 All-Cause Mortality

A time-to-event analysis evaluated risk for death from any cause (i.e., All-Cause Mortality). Survival status was unknown for 1.0% of subjects (n = 95).

No statistically significant or clinically meaningful difference was observed between the treatment groups (Table 29). The result, depicted by KM curves (Figure 19), demonstrates that the death rate was fairly constant over time in both treatment groups.

The event rate for All-Cause Mortality was 1.89 per 100 person-years for the placebo group and 1.96 per 100 person-years for the sibutramine group.

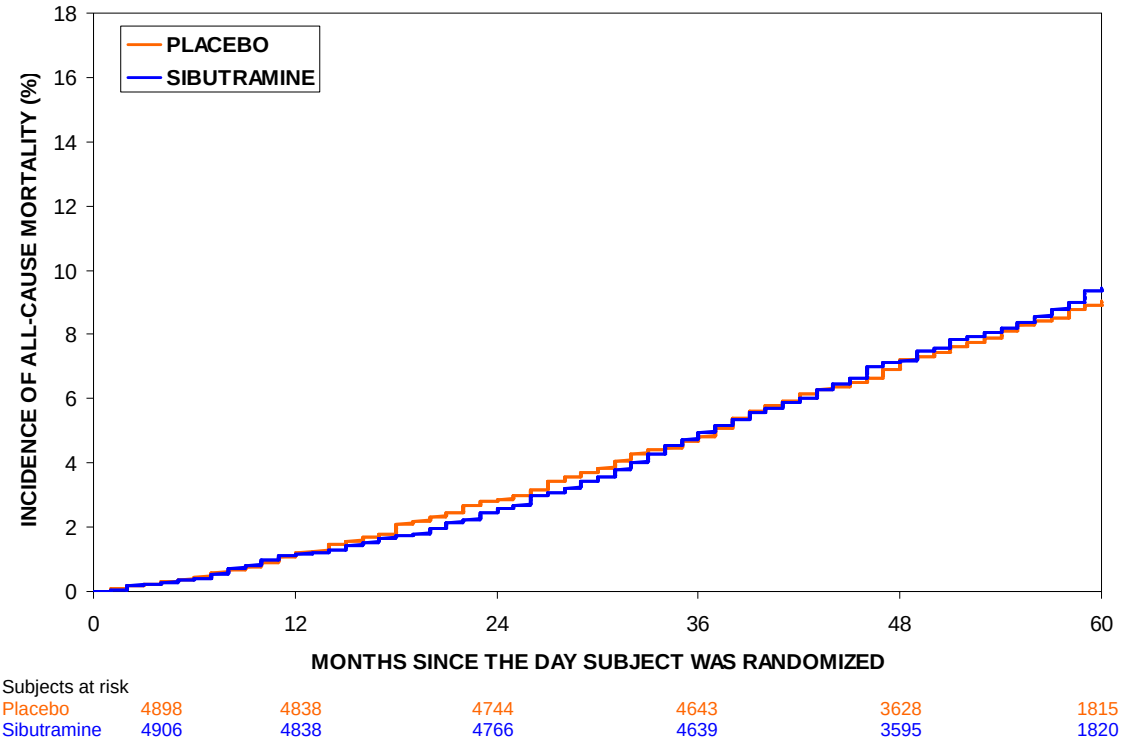
Table 29. All-Cause Mortality: ITT Population

	Placebo	Sibutramine	HR[a]	95% CI	*P* value[b]
Death from any cause	404 (8.2%)	418 (8.5%)	1.043	0.910, 1.196	0.543
Event rate per 100 person-years	1.89	1.96			

a. HR is for treatment effect.

b. The *P* value is from a Cox proportional hazards model adjusted for country, gender, and age at Lead-in Period Baseline.

Figure 19. Kaplan-Meier Curves of All-Cause Mortality: ITT Population



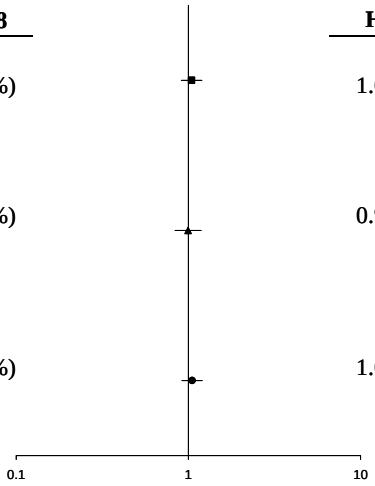
5.4.2.1 Sensitivity Analyses for All-Cause Mortality

Two sensitivity analyses confirmed the All-Cause Mortality result (Figure 20). These were:

- Analysis of only deaths that occurred on study drug (during the Treatment Period)
- Analysis of all deaths, including those occurring after the last subject's last visit date (27 March 2009)

Figure 20. Sensitivity Analyses for All-Cause Mortality: ITT Population

Analysis	Number (%) with endpoint: Sibutramine N = 4906	Number (%) with endpoint: Placebo N = 4898	HR	95% CI	*P* value
All-cause mortality	418 (8.5%)	404 (8.2%)	1.043	0.910, 1.196	0.543
Including only deaths during Treatment Period	256 (5.2%)	254 (5.2%)	0.996	0.837, 1.185	0.965
Including all deaths after LPLV	424 (8.6%)	407 (8.3%)	1.050	0.917, 1.203	0.481

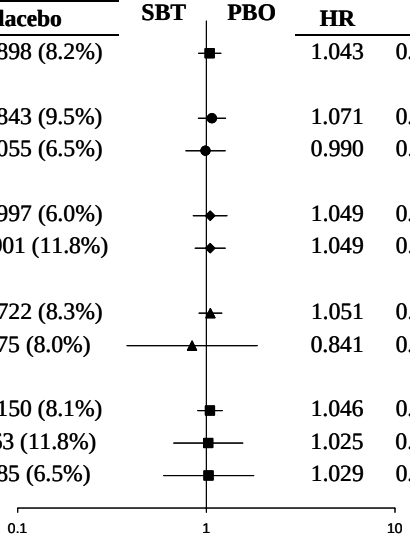


5.4.2.2 Subgroup Analyses for All-Cause Mortality

Additional time-to-event analyses evaluated risk for death of any cause within subgroups defined by gender, age, race, or geographic region of study conduct. No clinically relevant differences were noted for any of these subgroups (Figure 21).

Figure 21. All-Cause Mortality Results in Subgroups: ITT Population

Analysis	Number (%) with endpoint Sibutramine	Placebo	HR	95% CI	*P* value
ITT	418/4906 (8.5%)	404/4898 (8.2%)	1.043	0.910, 1.196	0.543
Gender					
Male	284/2807 (10.1%)	271/2843 (9.5%)	1.071	0.907, 1.265	0.419
Female	134/2099 (6.4%)	133/2055 (6.5%)	0.990	0.779, 1.259	0.938
Age					
< 65 years	187/3040 (6.2%)	179/2997 (6.0%)	1.049	0.854, 1.288	0.648
≥ 65 years	231/1866 (12.4%)	225/1901 (11.8%)	1.049	0.873, 1.261	0.608
Race					
Caucasian	407/4733 (8.6%)	390/4722 (8.3%)	1.051	0.915, 1.208	0.483
Non-Caucasian	11/172 (6.4%)	14/175 (8.0%)	0.841	0.380, 1.861	0.668
Geographic region					
Europe	349/4160 (8.4%)	336/4150 (8.1%)	1.046	0.901, 1.216	0.552
Central/South America	43/362 (11.9%)	43/363 (11.8%)	1.025	0.671, 1.564	0.910
Australia	26/384 (6.8%)	25/385 (6.5%)	1.029	0.594, 1.783	0.918



SBT= sibutramine; PBO = placebo

The age range for the ITT population was 51 to 88 years.

Interaction *P* values were not significant for any subgroup.

5.4.2.3 Cardiovascular and Noncardiovascular Deaths

All deaths were adjudicated as cardiovascular (CV) or noncardiovascular (non-CV) deaths by the SCOUT EAC. All CV Deaths were further classified into one of 10 prespecified categories of CV Death by the EAC (definitions included in Appendix E). Approximately 9% of all deaths had insufficient information available to be definitively classified as CV or non-CV death. These deaths were conservatively classified as CV death of unknown cause.

The risk for cardiovascular death events was similar in the sibutramine and placebo groups (Figure 22). The event rate for CV Death was low: 1.27 per 100 person-years for the placebo group and 1.24 per 100 person-years for the sibutramine group.

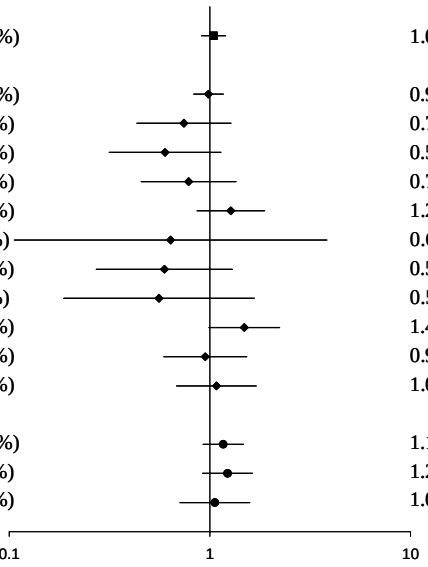
The incidence of non-CV death events was low in both the sibutramine group (3.1%) and the placebo group (2.7%). Likewise, the event rate for non-CV deaths was low in both

treatment groups (0.623 per 100 person-years for the placebo group and 0.716 per 100 person-years for the sibutramine group).

The majority of the non-CV deaths (66%) were attributed to cancer. Many different types of cancers were reported across both treatment groups. Additionally, there were 3 subjects (2 on placebo and 1 on sibutramine) who committed suicide.

Figure 22. Cardiovascular and Noncardiovascular Deaths: ITT Population

Analysis	Number (%) with endpoint: Sibutramine N = 4906	Placebo N = 4898	HR	95% CI	*P* value
All-cause mortality	418 (8.5%)	404 (8.2%)	1.043	0.910, 1.196	0.543
CV death	265 (5.4%)	271 (5.5%)	0.984	0.831, 1.166	0.852
Fatal MI	23 (0.5%)	31 (0.6%)	0.743	0.433, 1.275	0.281
Fatal stroke	15 (0.3%)	25 (0.5%)	0.598	0.315, 1.134	0.115
Heart failure	23 (0.5%)	30 (0.6%)	0.783	0.455, 1.348	0.378
Sudden death	58 (1.2%)	46 (0.9%)	1.272	0.864, 1.873	0.223
Fatal arrhythmia	2 (0.0%)	3 (0.1%)	0.637	0.106, 3.831	0.622
Invasive procedures	10 (0.2%)	17 (0.3%)	0.594	0.272, 1.297	0.191
AA + rupture or PE	5 (0.1%)	9 (0.2%)	0.558	0.187, 1.666	0.296
Presumed CV causes	58 (1.2%)	39 (0.8%)	1.484	0.989, 2.228	0.057
Unwitnessed, unexpected	33 (0.7%)	35 (0.7%)	0.948	0.589, 1.526	0.827
Unknown cause	38 (0.8%)	36 (0.7%)	1.078	0.683, 1.701	0.747
Non-CV death	153 (3.1%)	133 (2.7%)	1.167	0.925, 1.472	0.193
Cancer	104 (2.1%)	86 (1.8%)	1.226	0.921, 1.631	0.163
Non-cancer	49 (1.0%)	47 (1.0%)	1.059	0.710, 1.580	0.779



5.4.3 Cardiovascular Outcome Events During the Lead-in Period

During the Lead-in Period all subjects (N = 10,744) were treated with sibutramine. Eighteen subjects (0.17%) experienced a POE during the Lead-in Period, including 4 CV Deaths. The event rate for POE during the Lead-in Period was 1.44 per 100 person-years, which is lower than the event rate for POE for both the placebo and sibutramine groups after randomization (2.36 and 2.72 per 100 person-years, respectively). This suggests that short-term sibutramine treatment of all SCOUT

subjects, including those who met the exclusion criteria for outlier blood pressure or pulse did not result in increased risk for cardiovascular outcome events.

Table 30. POE During the Lead-in Period: Lead-in Period Safety Population

Outcome Event	N = 10,744 n (%)
Primary outcome event	18 (0.17)
Nonfatal MI	10 (0.09)
Nonfatal stroke	4 (0.04)
Resuscitated cardiac arrest	0
CV Death	4 (0.04)
Noncardiovascular death	0
All-cause mortality	4 (0.04)

5.4.4 Cardiovascular Outcome Events by Dose Titration

Investigators were permitted to increase the dose of study drug (from 10 mg to 15 mg daily) at any time (after randomization) for weight gain or inadequate weight loss. Investigators were instructed to take blood pressure and pulse changes into consideration before increasing the dose of study drug. The dose of study drug could later be decreased (from 15 mg to 10 mg daily) at any time at the discretion of the investigator.

Overall, 40.3% of placebo-treated subjects and 32.9% of sibutramine-treated subjects were titrated to the 15 mg dose (Table 31). In the sibutramine group, 81.1% (n = 1,308) of these subjects were permanently titrated to 15 mg sibutramine.

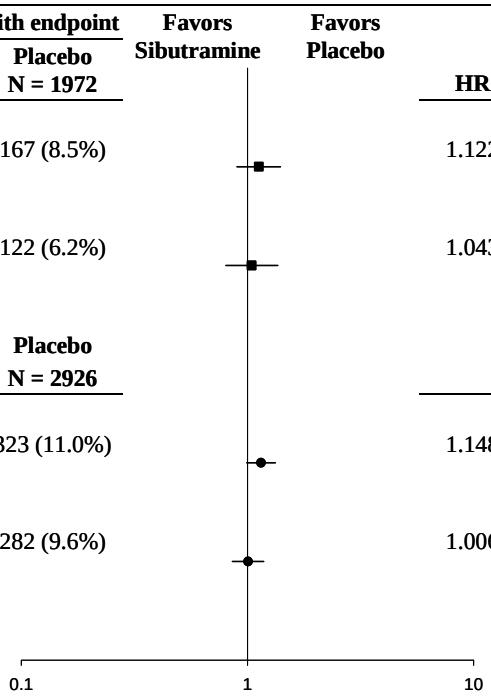
Table 31. Summary of Exposure to 15 mg Study Drug During the Randomization Phase: ITT Population

	Subjects Who Received 15 mg Dose	Duration on 15 mg Dose of Study Drug, days		
		Mean	(SD)	Range
Placebo, N = 4898	1972 (40.3%)	890.4	530.30	6 – 2001
	Subjects Who Received 15 mg Dose Permanently 1673 (34.2%)	964.1	500.69	6 – 2001
Sibutramine, N = 4906	1613 (32.9%)	802.4	499.95	5 – 2075
	Subjects Who Received 15 mg Dose Permanently 1308 (26.7%)	902.0	466.93	5 – 2075

The risk of POE or All-Cause Mortality was lower in the subgroups of subjects who were treated with the 15 mg dose of study drug (POE: sibutramine 9.2%, placebo 8.5%) as compared to those treated with the 10 mg dose only (POE: sibutramine 12.5%, placebo 11.0%) (Figure 23).

Figure 23. Results for Cardiovascular Outcome Events by 15 mg Dose Usage Subgroups: ITT Population

Analysis	Number (%) with endpoint: Sibutramine N = 1613	Placebo N = 1972	HR	95% CI	*P* value
Used 15 mg					
POE	149 (9.2%)	167 (8.5%)	1.122	0.899, 1.400	0.310
All-cause mortality	101 (6.3%)	122 (6.2%)	1.043	0.801, 1.360	0.753
	Sibutramine N = 3293	**Placebo N = 2926**			
Never used 15 mg					
POE	412 (12.5%)	323 (11.0%)	1.148	0.992, 1.328	0.064
All-cause mortality	317 (9.6%)	282 (9.6%)	1.006	0.857, 1.181	0.940



5.4.5 Cardiovascular Outcome Events by Cardiovascular Risk Group

As previously noted, all subjects were categorized into 1 of 3 protocol-specified CV risk groups (DM Only, CV Only, and CV + DM) based on their medical history and standard clinical evaluations (Section 5.2.2.2).

The CV risk groups were intended to classify subjects according to their potential level of CV risk; the highest risk group was the CV + DM group, while the lowest risk group was the DM Only group:

- The CV Only and CV + DM groups included subjects with known preexisting cardiovascular diseases (coronary artery disease, cerebrovascular disease, or PAOD) that met strict criteria stipulated in the study protocol, and

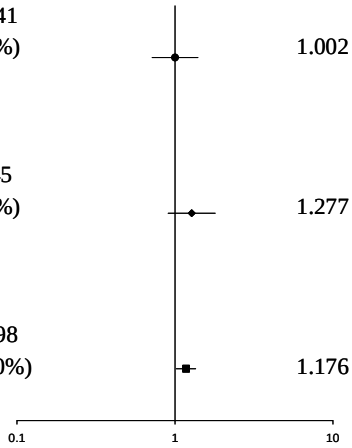
- The DM Only group included subjects that did not meet these strict criteria for the preexisting cardiovascular diseases.

The majority (61.5%) of subjects were classified in the CV + DM group. Analyses based on CV risk group assignment were prespecified in the statistical analysis plan. Although randomization was not stratified by CV risk group, baseline demographic and disease characteristics were well balanced between the treatment groups within all 3 CV risk groups.

Time-to-event analyses of the POE were performed by CV risk group. The increased risk for POE in the sibutramine group relative to the placebo group was observed in the CV Only and CV + DM groups. In contrast, no increased risk for POE was observed in the DM Only group (Figure 24).

Figure 24. Primary Outcome Events for CV Risk Groups: ITT Population

Group	Number (%) with endpoint		Favors SBT	Favors PBO	HR	95% CI	*P* value	Interaction *P* value
	Sibutramine	Placebo						
DM Only	N = 1151 69 (6.0%)	N = 1141 70 (6.1%)			1.002	0.718, 1.398	0.992	0.560
CV Only	N = 722 73 (10.1%)	N = 745 61 (8.2%)			1.277	0.907, 1.798	0.161	
CV + DM	N = 3016 418 (13.9%)	N = 2998 359 (12.0%)			1.176	1.021, 1.354	0.024	

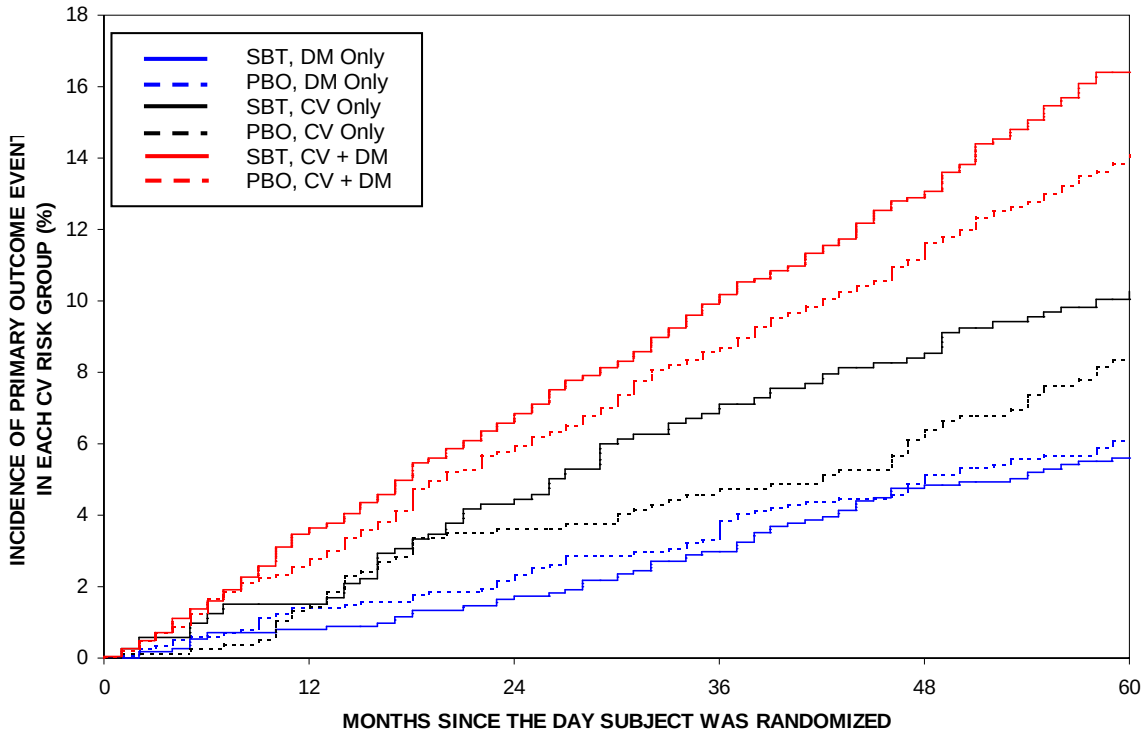


SBT = sibutramine; PBO = placebo

These results, depicted by KM curves (Figure 25), show the gradient of risk for POE with sibutramine across the CV risk groups. As expected, the incidence of POE was lowest in the DM Only group (6.1%; 1.237 events per 100 person-years), higher in the CV Only

group (9.1%; 2.172 events per 100 person-years), and highest in the CV + DM group (12.9%; 3.603 events per 100 person-years) (including both treatment groups).

Figure 25. Kaplan-Meier Curves of POE Results by CV Risk Groups: ITT Population



Number at risk	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Placebo, DM Only	1141	1121	1108	1088	1043	850
Sibutramine, DM Only	1151	1133	1122	1100	1053	853
Placebo, CV Only	745	731	710	696	675	450
Sibutramine, CV Only	722	708	684	660	639	421
Placebo, CV + DM	2998	2910	2791	2684	1735	418
Sibutramine, CV + DM	3016	2891	2779	2651	1695	434

Note: Plots have been truncated at Month 60 for graphical purposes. All data were included in the analysis.

Increased risk for POE in the sibutramine group relative to the placebo group was observed early and consistently across time in the CV Only and CV + DM groups. In contrast, for the DM Only group, lower risk for POE was observed in the sibutramine

group relative to the placebo group through year 5 of the study period (Figure 25). These observations are supported both by diagnostic log-log plots (Appendix G), in which the risk of sibutramine versus placebo for POE is not constant over time for the DM Only group, and by statistical tests of the treatment-by-subgroup interaction at yearly intervals (Table 32).

These results reinforce the potential for a treatment-by-CV risk group interaction with respect to yearly intervals and support the use of separate analyses of the POE for the DM Only group, irrespective of the nonsignificant ($P = 0.56$) overall treatment-by-CV risk group interaction (Figure 24). It is important to note that this interaction P value was influenced both by events at the end of the study, when fewer subjects were at risk, and by the fact that only 13% of the POEs occurred in the DM Only group. Importantly, the interaction P values based on earlier time points are more in line with the expected interaction based on appearance of these curves.

The DM Only group, which has the lowest POE rate of the 3 CV risk groups, consists of subjects with no known history of cardiovascular disease and is also the risk group most similar to the indicated population. The DM Only group, notably, has a risk profile over time that is distinct from the other 2 CV risk groups, which warrants separate evaluation of this risk group.

Table 32. Cumulative Number (%) of Subjects Experiencing First POE by CV Risk Group: ITT Population

POE	Placebo	Sibutramine	Hazard Ratio	95% CI	*P* value[a]	Interaction *P* value[b]
DM Only	N = 1141	N = 1151				
3 mo	3 (0.3%)	2 (0.2%)	0.874	0.141, 5.408	0.885	
6 mo	7 (0.6%)	7 (0.6%)	1.122	0.392, 3.210	0.830	
12 mo	16 (1.4%)	9 (0.8%)	0.599	0.264, 1.356	0.219	0.021*
24 mo	26 (2.3%)	20 (1.7%)	0.789	0.440, 1.415	0.427	0.104
36 mo	44 (3.9%)	34 (3.0%)	0.782	0.500, 1.225	0.283	0.011*
48 mo	58 (5.1%)	55 (4.8%)	0.966	0.667, 1.397	0.852	0.112
60 mo	68 (6.0%)	65 (5.6%)	0.971	0.690, 1.365	0.864	0.094*
POE overall	70 (6.1%)	69 (6.0%)	1.002	0.718, 1.398	0.992	
CV Only	N = 745	N = 722				
3 mo	1 (0.1%)	4 (0.6%)	4.398	0.483, 40.049	0.189	
6 mo	2 (0.3%)	8 (1.1%)	4.632	0.977, 21.963	0.054	
12 mo	10 (1.3%)	11 (1.5%)	1.219	0.516, 2.882	0.652	
24 mo	27 (3.6%)	32 (4.4%)	1.312	0.784, 2.194	0.302	
36 mo	35 (4.7%)	51 (7.1%)	1.567	1.017, 2.414	0.042	
48 mo	48 (6.4%)	62 (8.6%)	1.385	0.948, 2.023	0.092	
60 mo	60 (8.1%)	72 (10.0%)	1.281	0.908, 1.808	0.159	
POE overall	61 (8.2%)	73 (10.1%)	1.277	0.907, 1.798	0.161	
CV + DM	N = 2998	N = 3016				
3 mo	18 (0.6%)	18 (0.6%)	1.008	0.524, 1.939	0.980	
6 mo	46 (1.5%)	45 (1.5%)	0.980	0.650, 1.479	0.924	
12 mo	83 (2.8%)	109 (3.6%)	1.316	0.989, 1.751	0.060	
24 mo	178 (5.9%)	201 (6.7%)	1.133	0.926, 1.386	0.225	
36 mo	259 (8.6%)	304 (10.1%)	1.183	1.002, 1.396	0.047	
48 mo	330 (11.0%)	376 (12.5%)	1.152	0.993, 1.335	0.061	
60 mo	355 (11.8%)	415 (13.8%)	1.182	1.025, 1.361	0.021	
POE overall	359 (12.0%)	418 (13.9%)	1.176	1.021, 1.354	0.024	

a. Within–time interval comparisons for difference between treatment groups.

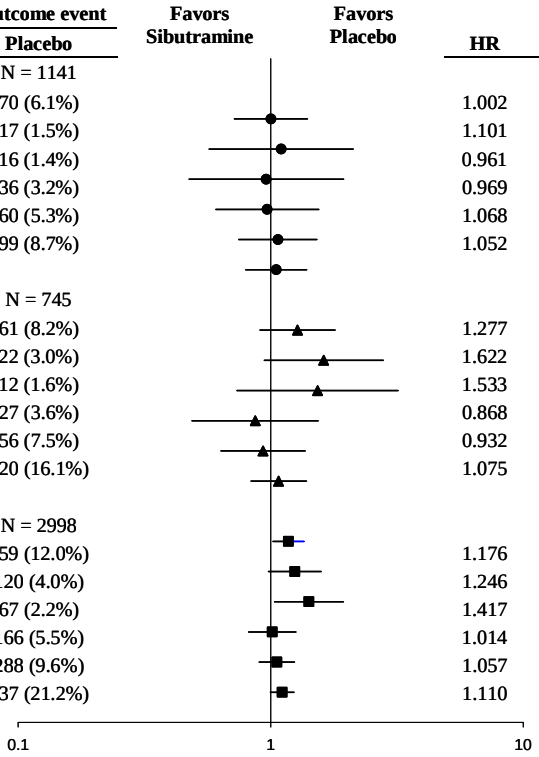
b. Test of treatment-by-subgroup (DM Only vs. other groups combined) interaction, based on Kaplan-Meier estimates and their standard errors at yearly intervals (Appendix G).

* Statistically significant at the 2-sided 0.10 level.

Additional time-to-event analyses by CV risk group (Figure 26) further confirmed that the increased risk for POE in the sibutramine group was attributed to nonfatal events of MI and stroke in the CV + DM and CV Only groups. No difference in risk of CV Death between the treatment groups was observed in any of the CV risk groups.

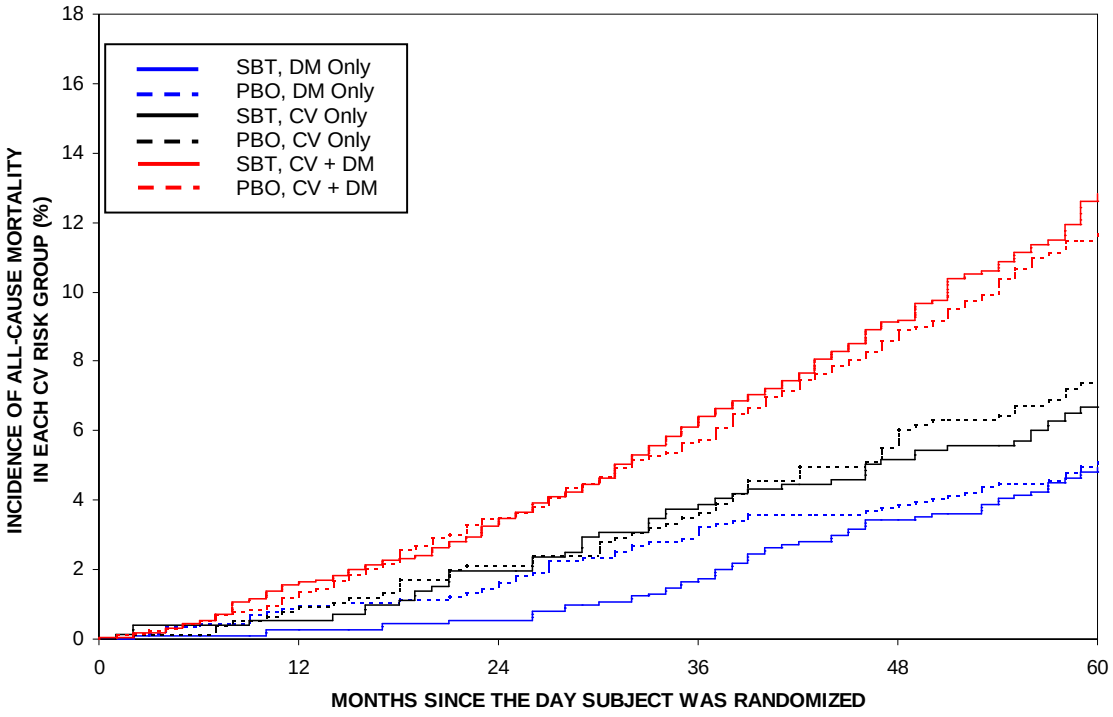
Figure 26. Outcome Events for CV Risk Groups: ITT Population

Analysis	Number (%) with outcome event: Sibutramine	Number (%) with outcome event: Placebo	HR	95% CI	*P* value
DM Only Group	N = 1151	N = 1141			
POE	69 (6.0%)	70 (6.1%)	1.002	0.718, 1.398	0.992
Nonfatal MI	19 (1.7%)	17 (1.5%)	1.101	0.571, 2.123	0.774
Nonfatal stroke	15 (1.3%)	16 (1.4%)	0.961	0.475, 1.944	0.912
CV death	34 (3.0%)	36 (3.2%)	0.969	0.606, 1.551	0.896
All-cause mortality	62 (5.4%)	60 (5.3%)	1.068	0.748, 1.524	0.719
POE + revascularization	102 (8.9%)	99 (8.7%)	1.052	0.797, 1.388	0.721
CV Only Group	N = 722	N = 745			
POE	73 (10.1%)	61 (8.2%)	1.277	0.907, 1.798	0.161
Nonfatal MI	33 (4.6%)	22 (3.0%)	1.622	0.943, 2.790	0.081
Nonfatal stroke	18 (2.5%)	12 (1.6%)	1.533	0.736, 3.195	0.254
CV death	21 (2.9%)	27 (3.6%)	0.868	0.488, 1.543	0.629
All-cause mortality	50 (6.9%)	56 (7.5%)	0.932	0.635, 1.369	0.721
POE + revascularization	124 (17.2%)	120 (16.1%)	1.075	0.836, 1.384	0.572
CV + DM Group	N = 3016	N = 2998			
POE	418 (13.9%)	359 (12.0%)	1.176	1.021, 1.354	0.024
Nonfatal MI	148 (4.9%)	120 (4.0%)	1.246	0.980, 1.586	0.073
Nonfatal stroke	94 (3.1%)	67 (2.2%)	1.417	1.036, 1.939	0.029
CV death	167 (5.5%)	166 (5.5%)	1.014	0.818, 1.257	0.900
All-cause mortality	305 (10.1%)	288 (9.6%)	1.057	0.900, 1.242	0.498
POE + revascularization	700 (23.2%)	637 (21.2%)	1.110	0.997, 1.236	0.056



For the CV Only or the CV + DM groups no differences were observed between the treatment groups for All-Cause Mortality. For the DM Only group, the risk of All-Cause Mortality was substantially lower for sibutramine than for placebo well beyond the first 3 years of treatment (Figure 27 and Table 33). These results further illustrate the differential risk profile in the DM Only group.

Figure 27. Kaplan-Meier Curves of All-Cause Mortality by CV Risk Groups: ITT Population



Number at risk	Baseline	Month 12	Month 24	Month 36	Month 48	Month 60
Placebo, DM Only	1141	1129	1122	1104	1067	875
Sibutramine, DM Only	1151	1141	1136	1120	1079	879
Placebo, CV Only	745	738	727	716	699	475
Sibutramine, CV Only	722	717	705	690	676	452
Placebo, CV + DM	2998	2957	2881	2809	1848	453
Sibutramine, CV + DM	3016	2963	2909	2813	1824	477

Note: Plots have been truncated at Month 60 for graphical purposes. All data were included in the analysis.

Table 33. Cumulative Number (%) of Subjects for All-Cause Mortality by CV Risk Group: ITT Population

	Placebo	Sibutramine	Hazard Ratio	95% CI	*P* value[a]	Interaction *P* value[b]
DM Only	N = 1141	N = 1151				
3 mo	2 (0.2%)	1 (0.1%)	0.772	0.062, 9.650	0.841	
6 mo	4 (0.4%)	1 (0.1%)	0.287	0.032, 2.580	0.265	
12 mo	10 (0.9%)	3 (0.3%)	0.310	0.085, 1.128	0.076	0.044*
24 mo	18 (1.6%)	6 (0.5%)	0.340	0.135, 0.858	0.022	0.116
36 mo	37 (3.2%)	20 (1.7%)	0.560	0.325, 0.966	0.037	0.014*
48 mo	44 (3.9%)	39 (3.4%)	0.920	0.597, 1.417	0.705	0.552
60 mo	57 (5.0%)	57 (5.0%)	1.034	0.716, 1.494	0.858	0.678
Overall	60 (5.3%)	62 (5.4%)	1.068	0.748, 1.524	0.719	
CV Only	N = 745	N = 722				
3 mo	1 (0.1%)	3 (0.4%)	2.924	0.297, 28.739	0.358	
6 mo	1 (0.1%)	3 (0.4%)	2.924	0.297, 28.739	0.358	
12 mo	7 (0.9%)	4 (0.6%)	0.598	0.174, 2.051	0.414	
24 mo	16 (2.1%)	14 (1.9%)	0.931	0.453, 1.913	0.845	
36 mo	27 (3.6%)	28 (3.9%)	1.100	0.646, 1.872	0.726	
48 mo	45 (6.0%)	38 (5.3%)	0.904	0.585, 1.396	0.649	
60 mo	54 (7.2%)	47 (6.5%)	0.914	0.617, 1.355	0.655	
Overall	56 (7.5%)	50 (6.9%)	0.932	0.635, 1.369	0.721	
CV + DM	N = 2998	N = 3016				
3 mo	5 (0.2%)	6 (0.2%)	1.223	0.372, 4.017	0.740	
6 mo	15 (0.5%)	14 (0.5%)	0.944	0.455, 1.958	0.877	
12 mo	39 (1.3%)	50 (1.7%)	1.291	0.849, 1.963	0.232	
24 mo	105 (3.5%)	102 (3.4%)	0.969	0.738, 1.273	0.821	
36 mo	173 (5.8%)	193 (6.4%)	1.117	0.909, 1.371	0.292	
48 mo	253 (8.4%)	266 (8.8%)	1.055	0.888, 1.254	0.539	
60 mo	282 (9.4%)	302 (10.0%)	1.071	0.911, 1.260	0.405	
Overall	288 (9.6%)	305 (10.1%)	1.057	0.900, 1.242	0.498	

a. Within–time interval comparisons for difference between treatment groups.

b. Test of treatment-by-subgroup (DM Only vs. other groups combined) interaction, based on Kaplan-Meier estimates and their standard errors at yearly intervals (Appendix G).

* Statistically significant at the 2-sided 0.10 level.

5.4.6 SCOUT Analyses of Relationship of Vital Sign Changes and Weight Loss Response to POE

The following sections review these analyses:

- Relationship between vital sign changes and risk for POE
- Relationship between weight loss and risk for POE
- Relationship between both vital sign changes and weight loss and risk for POE

5.4.6.1 Primary Outcome Events by Vital Sign Findings

Exploratory analyses of SCOUT have indicated that, at a population level, both the absolute blood pressure and pulse, and changes in blood pressure and pulse are associated with an increased risk of POE.

The following prespecified and post hoc analyses further evaluated the relationship between CV outcome events and blood pressure and pulse findings by treatment group (sibutramine or placebo):

- Impact of baseline measurements of blood pressure or pulse,
- Impact of measurements over time (after randomization) of blood pressure or pulse as time-dependent covariates, and
- Impact of achieving potentially clinically relevant thresholds for blood pressure or pulse during the Lead-in Period or after randomization

Analyses based on vital sign thresholds, as discussed below, provide an understanding of the risk for CV outcome events in relation to potentially clinically relevant changes in vital signs in sibutramine-treated subjects.

An analysis was performed based on subjects with increases above baseline in SBP or DBP (≥ 10 mmHg) or pulse (≥ 10 bpm) at 2 consecutive study visits during the first 3 months of treatment or at the final visit (for those subjects who prematurely

discontinued study procedures on or before Month 3), including the 6 weeks of treatment during the Lead-in Period (designated as "Vital Signs Outliers," see below).

The rationale for this particular outlier analysis follows:

- These vital sign criteria are generally accepted, and were previously used in sibutramine studies to identify subjects early (within 3 months) with potentially clinically relevant changes in vital signs, and
- The vital sign criteria are consistent with European label recommendations regarding blood pressure and pulse monitoring for 2 consecutive increases (as defined above) and treatment discontinuation for those meeting these criteria

Therefore, time-to-event analyses were conducted to compare risk for cardiovascular outcome events between SCOUT Vital Signs Outliers and Vital Signs Non-Outliers (those who did not have these increases in blood pressure or pulse).

Of note, this analysis includes 550 subjects who developed elevations in systolic blood pressure (> 10 mmHg), diastolic blood pressure (> 10 mmHg), or pulse (> 10 bpm) at two consecutive study visits during the 6-week Lead-in Period.

The results of the POE analysis comparing the Vital Signs Outliers to the Vital Signs Non-Outliers for sibutramine and placebo groups are provided in Table 34.

Importantly, the results show that the sibutramine Vital Signs Non-Outliers (10.7%) have a lower risk of POE as compared to the sibutramine Vital Signs Outliers (12.7%) (HR = 0.864, 95% CI = 0.729–1.024). Similar results were seen for the CV risk groups. Therefore, labeling that recommends routine monitoring of vital signs during the first 3 months of treatment and discontinuation of those who meet outlier criteria would be expected to reduce the risk for CV outcome events.

In addition, the results show that even in this high-CV-risk population when comparing sibutramine Vital Signs Non-Outliers to the placebo Vital Signs Non-Outliers, no increased risk for POE is observed (HR = 1.047, 95% CI = 0.904–1.214). Of note,

similar findings are observed in the DM Only group when comparing sibutramine Vital Signs Non-Outliers to the placebo Vital Signs Non-Outliers (HR = 0.664, 95% CI = 0.417–1.057). This further supports the effectiveness of early monitoring for blood pressure and pulse changes with sibutramine use.

Table 34. POE Results by Vital Signs Outlier Status: ITT Population and CV Risk Groups

Analysis	Sibutramine Outliers	Sibutramine Non-Outliers	Placebo Outliers	Placebo Non-Outliers	Sibutramine Non-Outliers vs. Sibutramine Outliers HR (95% CI)	Sibutramine Non-Outliers vs. Placebo Non-Outliers HR (95% CI)
ITT population	221/1736 (12.7%)	340/3169 (10.7%)	120/1344 (8.9%)	370/3553 (10.4%)	0.864 (0.729, 1.024)	1.047 (0.904, 1.214)
CV + DM Group	149/974 (15.3%)	269/2042 (13.2%)	86/767 (11.2%)	273/2231 (12.2%)	0.880 (0.720, 1.075)	1.080 (0.912, 1.278)
CV Only Group	30/279 (10.8%)	43/443 (9.7%)	13/208 (6.3%)	48/537 (8.9%)	0.929 (0.582, 1.481)	1.146 (0.759, 1.732)
DM Only Group	41/475 (8.6%)	28/676 (4.1%)	21/367 (5.7%)	49/774 (6.3%)	0.482 (0.298, 0.779)	0.664 (0.417, 1.057)

Notes: The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for country, gender, and age at Lead-in Period Baseline.

Vital Signs Outliers were defined as subjects with increases above lead-in baseline in SBP or DBP (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment.

Several sensitivity analyses were performed and the results are consistent with the above findings. These analyses evaluated the following vital sign criteria:

- Absolute thresholds:
  - Assessment of subjects with measures of SBP ≥ 140 mmHg, or DBP ≥ 90 mmHg, or pulse ≥ 90 bpm, on 2 consecutive study visits during the first 3 months of treatment or at the final visit for those subjects who prematurely discontinued study procedures on or before Month 3.
    - Using this definition, sibutramine Vital Signs Non-Outliers (10.8%) have a lower risk of POE as compared to the sibutramine Vital Signs Outliers (12.1%) (HR = 0.915, 95% CI = 0.774–1.081).

- Assessment of subjects with measures of SBP ≥ 150 mmHg, or DBP ≥ 100 mmHg, or pulse ≥ 90 bpm, on 2 consecutive study visits during the first 3 months of treatment or at the final visit for those subjects who prematurely discontinued study procedures on or before Month 3.
  - Using this definition, sibutramine Vital Signs Non-Outliers (10.6%) have a lower risk of POE as compared to the sibutramine Vital Signs Outliers (13.8%) (HR = 0.780, 95% CI = 0.653–0.933).
- Assessment of subjects with measures of SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or pulse ≥ 100 bpm, on 2 consecutive study visits during the first 3 months of treatment or at the final visit for those subjects who prematurely discontinued study procedures on or before Month 3.
  - Using this definition, sibutramine Vital Signs Non-Outliers (11.1%) have a lower risk of POE as compared to the sibutramine Vital Signs Outliers (11.8%) (HR = 0.983, 95% CI = 0.833–1.161).

- Rate-pressure product:
  - Assessment of subjects with rate-pressure product (calculated by SBP•pulse/100) ≥ 125 mmHg•bpm on 2 consecutive study visits during the first 3 months of treatment or at the final visit for those subjects who prematurely discontinued study procedures on or before Month 3.
    - Using this definition, sibutramine Vital Signs Non-Outliers (11.2%) have a lower risk of POE as compared to the sibutramine Vital Signs Outliers (12.8%) (HR = 0.870, 95% CI = 0.682–1.111).

5.4.6.2 Cardiovascular Outcome Events by Weight Loss Responders

An important study design feature in SCOUT was the continuation of treatment with study drug, irrespective of weight loss. This is inconsistent with standard clinical practice and global labeling directions for sibutramine recommending the discontinuation of therapy in patients who do not achieve adequate weight loss. Furthermore, patients who achieve an adequate amount of weight loss (at least 5% of initial body weight) with sibutramine therapy can be identified early (within 3 months of initiating therapy). Notably, the European sibutramine summary of product characteristics (SmPC) directs

discontinuation of sibutramine in patients who do not achieve at least 5% weight loss by 3 months of therapy.

In order to understand the relationship between weight loss and the risk for POE, a post hoc analysis was conducted to look at the proportion of subjects in the SCOUT study who had at least 5% weight loss after 3 months of treatment. These subjects were classified as Weight Loss Responders. Weight Loss Nonresponders did not meet this criterion.

Post hoc analyses were conducted to compare risk for POE between Weight Loss Responders and Weight Loss Nonresponders.

The results showed a lower incidence of POE in sibutramine Weight Loss Responders (9.5%) compared to sibutramine Weight Loss Nonresponders (12.3%) (HR = 0.808, 95% CI = 0.668–0.979). Labeling that recommends discontinuation of sibutramine in subjects who fail to achieve at least 5% weight loss by the first 3 months of treatment would be expected to reduce the risk for CV outcome events.

When the CV risk groups are evaluated, the CV Only and CV + DM groups showed a higher incidence of POE in the sibutramine Weight Loss Responders as compared to placebo Weight Loss Responders. Thus, amongst the higher CV risk subjects in SCOUT, placebo Weight Loss Responders were at lower risk than sibutramine Weight Loss Responders.

However, for the DM Only group, the results showed no increased risk for POE in sibutramine Weight Loss Responders (6.0%) compared to placebo Weight Loss Responders (6.3%) (HR = 0.966, 95% CI = 0.493–1.891).

Table 35. POE Results by Weight Loss Responder Status: ITT Population and CV Risk Groups

Analysis	Sibutramine Nonresponder	Sibutramine Responder	Placebo Nonresponder	Placebo Responder	Sibutramine Responder vs. Sibutramine Nonresponder HR (95% CI)	Sibutramine Responder vs. Placebo Responder HR (95% CI)
ITT population	419/3415 (12.3%)	142/1491 (9.5%)	415/3941 (10.5%)	75/957 (7.8%)	0.808 (0.668, 0.979)	1.231 (0.931, 1.629)
CV + DM Group	320/2156 (14.8%)	98/860 (11.4%)	309/2447 (12.6%)	50/551 (9.1%)	0.768 (0.612, 0.964)	1.253 (0.891, 1.761)
CV Only Group	51/460 (11.1%)	22/262 (8.4%)	50/566 (8.8%)	11/179 (6.1%)	0.818 (0.492, 1.359)	1.477 (0.713, 3.062)
DM Only Group	47/787 (6.0%)	22/364 (6.0%)	56/917 (6.1%)	14/224 (6.3%)	1.119 (0.672, 1.863)	0.966 (0.493, 1.891)

Notes: Weight Loss Responders were defined as subjects who lost at least 5% of their baseline weight at Month 1 and/or Month 2 of the double-blind Treatment Period.

The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for gender and age at Lead-in Period Baseline.

Importantly, 70% of the sibutramine-treated subjects in SCOUT did not achieve at least 5% weight loss after 3 months of treatment and were continued on treatment for up to 6 years. These subjects, therefore, were not receiving the benefits of sibutramine-induced weight loss but continued to be exposed to the risk of sibutramine's potential effects on blood pressure and pulse.

Two sensitivity analyses were performed and the results are consistent with the findings reviewed above. These analyses evaluated weight loss responders as follows:

- "Weight Loss Responders" defined as subjects achieving at least 5% weight loss by 2 months of treatment.
  - Using this definition, sibutramine Weight Loss Responders (9.0%) have a lower risk of POE as compared to the sibutramine Weight Loss Nonresponders (12.3%) (HR = 0.762, 95% CI = 0.622–0.934).

- "Weight Loss Responders" defined as subjects achieving at least 5% weight loss by 6 months of treatment
  - Using this definition, sibutramine Weight Loss Responders (9.9%) have a lower risk of POE as compared to the sibutramine Weight Loss Nonresponders (12.3%) (HR = 0.813, 95% CI = 0.680–0.972).

5.4.6.3 Cardiovascular Outcome Events by Vital Signs Outliers and Weight Loss Responders

Another post hoc analysis compared the subjects (designated "Weight Loss/Vital Signs Conformers") who were Weight Loss Responders AND who did not meet criteria for vital signs outliers (Vital Signs Non-Outliers) to subjects who were either Weight Loss Nonresponders and/or Vital Signs Outliers ("Weight Loss/Vital Signs Nonconformers").

The results of the POE analysis comparing the Weight Loss/Vital Signs Conformers to the Weight Loss/Vital Signs Nonconformers for the sibutramine and placebo groups are provided in Table 36.

Importantly, the results show that the sibutramine Weight Loss/Vital Signs Conformers have a statistically significantly lower risk of POE (8.1%) as compared to the sibutramine Weight Loss/Vital Signs Nonconformers (12.3%) (HR = 0.673, 95% CI = 0.532–0.853). Similar results are seen for the CV risk groups. Therefore, labeling that recommends the following would identify patients who would be appropriate for continued therapy.

- Discontinuation of treatment in patients who have 2 consecutive increases in blood pressure or pulse in the first 3 months of therapy, and
- Discontinuation of treatment in patients who do not achieve at least 5% weight loss in the first 3 months of therapy.

In addition, the results show that even in this high-CV-risk population when comparing sibutramine Weight Loss/Vital Signs Conformers (8.1%) to the placebo Weight Loss/Vital Signs Conformers (7.9%) no difference in risk for POE is observed

(HR = 1.019, 95% CI = 0.727–1.428) (All Subjects). For the DM Only group, although the sample sizes are small, similar findings are observed (HR = 0.773, 95% CI = 0.304–1.966).

Table 36. POE Results by Weight Loss/Vital Signs Conformers Status: ITT Population and CV Risk Groups

Analysis	Sibutramine Weight Loss/Vital Signs Non-conformers	Sibutramine Weight Loss/Vital Signs Conformers	Placebo Weight Loss/Vital Signs Non-conformers	Placebo Weight Loss/Vital Signs Conformers	Sibutramine Weight Loss/Vital Signs Conformers vs. Sibutramine Weight Loss/Vital Signs Nonconformers HR (95% CI)	Sibutramine Weight Loss/Vital Signs Conformers vs. Placebo Weight Loss/Vital Signs Conformers HR (95% CI)
ITT population	480/3900 (12.3%)	81/1006 (8.1%)	432/4160 (10.4%)	58/738 (7.9%)	0.673 (0.532, 0.853)	1.019 (0.727, 1.428)
CV + DM Group	363/2415 (15.0%)	55/601 (9.2%)	319/2562 (12.5%)	40/436 (9.2%)	0.602 (0.453, 0.800)	0.973 (0.647, 1.463)
CV Only Group	56/549 (10.2%)	17/173 (9.8%)	52/610 (8.5%)	9/135 (6.7%)	1.047 (0.604, 1.814)	1.573 (0.696, 3.556)
DM Only Group	60/922 (6.5%)	9/229 (3.9%)	61/976 (6.3%)	9/165 (5.5%)	0.655 (0.324, 1.323)	0.773 (0.304, 1.966)

Notes: The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for country, gender, and age at Lead-in Period Baseline.

Weight Loss/Vital Signs Conformers are subjects who were Weight Loss Responders *and* who did not meet criteria for vital signs outliers (i.e., were Vital Signs Non-Outliers)

5.4.6.3.1 Risk of POE in SCOUT During Initial 3 Months of Treatment

During the Lead-in Period, when all subjects received 6 weeks of sibutramine, a low rate of POE was observed with a total of 18 events (0.17%) (Section 5.4.3). During the first 2 months of the double-blind period of the study, the rate of POE in the sibutramine group was 0.3%. This indicates that a 3-month course of sibutramine, even in the high-CV-risk All Subject population, is associated with a low rate of outcome events (0.47%).

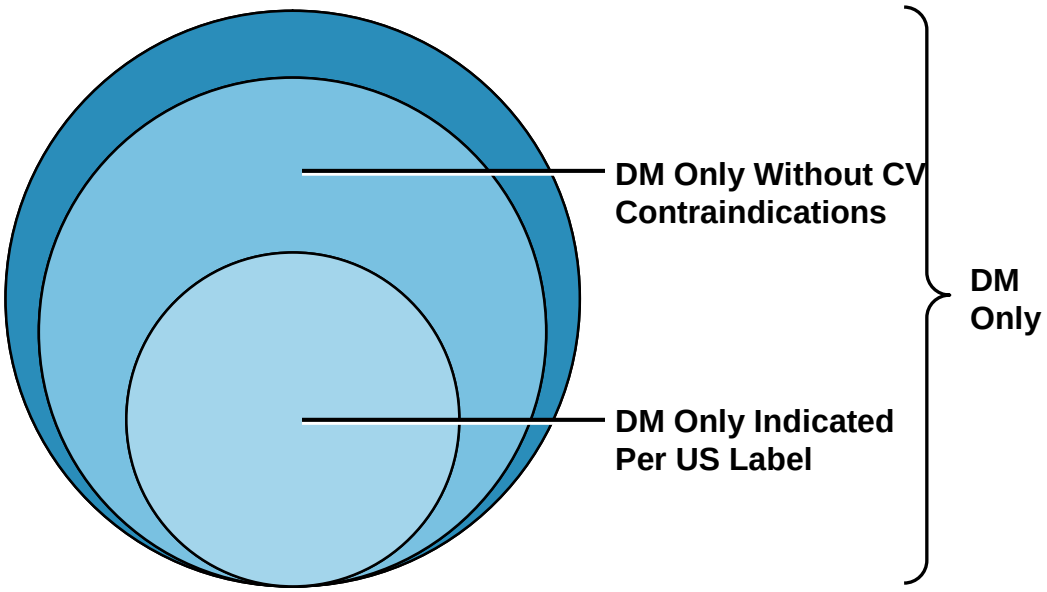
5.4.7 Subpopulations Similar to the Indicated Population

5.4.7.1 Definitions of the DM Only Subpopulations Similar to the Indicated Population

Of the 3 CV risk groups, the DM Only group is the group closest to the indicated population. Given this, a further evaluation of the DM Only group was performed to attempt to apply the findings from SCOUT to the indicated population (Figure 28).

- The DM Only group contains a small subset of subjects for whom treatment would be indicated per the current the US label. This subpopulation is referred to as "DM Only Indicated per US label."
  - Although this group is of primary interest its small size (N = 768) limits the interpretability of the results.
- Another approach was to evaluate a larger subset of the DM Only group (N = 1,789). This subpopulation is referred to as the "DM Only Without CV Contraindications subpopulation."
  - Although the DM Only group did not include subjects with a history of cardiovascular disease (e.g., MI or stroke), it did include some subjects with other CV conditions that are contraindicated in the US label (e.g., TIA, angina, and congestive heart failure). The DM Only Without CV Contraindications subpopulation, therefore, does not include any subjects with CV conditions contraindicated per US label. It does, however, include subjects with other contraindications such as age > 65 years and blood pressure > 145/90 mmHg.
  - The larger size of this subgroup allows for a more informative interpretation of the results, and included the majority of subjects in the DM Only group (78.05% [1,789 subjects]).

Figure 28. DM Only Group and Subpopulations



The following section presents analyses evaluating these DM Only subpopulations.

5.4.7.2 Evaluation of DM Only Subpopulation Similar to the Indicated Population

The DM Only group included a small number of subjects who were indicated for sibutramine treatment according to the current US label (n = 768; 7.8% of all SCOUT subjects [33.5% of DM Only subjects]). The key criteria used to identify these subjects are listed below:

- Age ≤ 65 years
- Blood pressure ≤ 145/90 mmHg
- Pulse ≤ 100 bpm
- BMI ≥ 27 kg/m^2
- No coronary artery disease

- No congestive heart failure
- No peripheral arterial occlusive disease
- No arrhythmia
- No cerebrovascular disease (stroke or TIA)

The event rate for POE in the DM Only Indicated per US Label subpopulation was 0.622 and 0.861 per 100 person-years for placebo and sibutramine, respectively (Table 37).

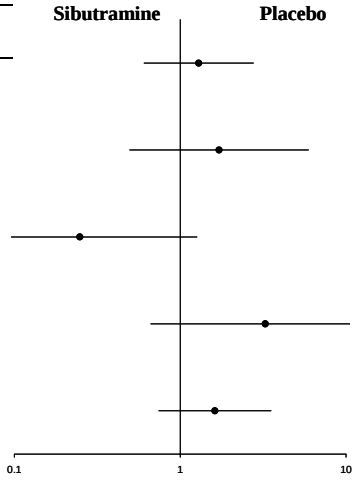
Table 37. POE Incidence and Event Rates for the DM Only Indicated per US Label Subpopulation: ITT Population

	Incidence of POE		POE Event Rate per 100 Person-Years	
DM Only Subpopulation	**Placebo**	**Sibutramine**	**Placebo**	**Sibutramine**
DM Only Indicated per US Label	12/390 (3.1%)	16/378 (4.2%)	0.622	0.861

The time-to-event analyses for POE, the individual components and All-Cause Mortality are shown in Figure 29. The potential increased risk of death (CV Death and All-Cause Mortality) with sibutramine compared to placebo is inconsistent with results from the DM Only group and with the study overall. Given the small number of subjects and low event rates in this subpopulation, the results have limited interpretability. Additionally, the difference in events rates in the DM Only Indicated per US Label subpopulation did not become apparent until later in the study, after 3 years of the study.

Figure 29. Results for DM Only Indicated per US Label Subpopulation

Analysis	Number (%) with outcome event: Sibutramine N = 378	Placebo N = 390	HR	95% CI	*P* value
POE	16 (4.2%)	12 (3.1%)	1.293	0.605, 2.763	0.508
Nonfatal MI	7 (1.9%)	4 (1.0%)	1.715	0.496, 5.931	0.394
Nonfatal stroke	2 (0.5%)	6 (1.5%)	0.248	0.049, 1.261	0.093
CV death	7 (1.9%)	2 (0.5%)	3.260	0.664, 15.994	0.145
All-cause mortality	16 (4.2%)	11 (2.8%)	1.619	0.743, 3.527	0.225

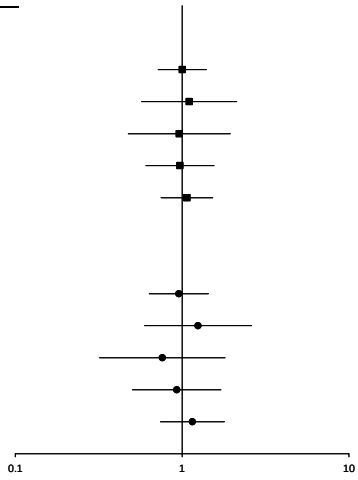


Note: Lower confidence limit not displayed for nonfatal stroke; upper confidence limit not displayed for CV death.

The POE incidence rate with sibutramine for the DM Only Without CV Contraindications subpopulation was 5.0%; the event rate was 1.032 events per 100 person-years. Results from time-to-event analyses (Figure 30) were similar to the results from the DM Only group and suggest that there was no increased risk for nonfatal or fatal events in these subjects without a history of the contraindicated cardiovascular conditions.

Figure 30. Results for DM Only Without CV Contraindications Subpopulation: ITT Population

Analysis	Number (%) with outcome event: Sibutramine	Placebo	HR	95% CI	*P* value
DM Only	N = 1151	N = 1141			
POE	69 (6.0%)	70 (6.1%)	1.002	0.718, 1.398	0.992
Nonfatal MI	19 (1.7%)	17 (1.5%)	1.101	0.571, 2.123	0.911
Nonfatal stroke	15 (1.3%)	16 (1.4%)	0.961	0.475, 1.945	0.912
CV death	34 (3.0%)	36 (3.2%)	0.969	0.606, 1.551	0.896
All-cause mortality	62 (5.4%)	60 (5.3%)	1.068	0.748, 1.524	0.719
DM Only without CV Contraindications	N = 893	N = 896			
POE	45 (5.0%)	48 (5.4%)	0.956	0.635, 1.438	0.828
Nonfatal MI	16 (1.8%)	13 (1.5%)	1.244	0.596, 2.598	0.561
Nonfatal stroke	9 (1.0%)	12 (1.3%)	0.762	0.321, 1.811	0.538
CV death	20 (2.2%)	22 (2.5%)	0.928	0.504, 1.707	0.810
All-cause mortality	42 (4.7%)	38 (4.2%)	1.152	0.741, 1.792	0.530



Increased risk for POE in the sibutramine group relative to the placebo group was observed early and consistently across time in the CV Only and CV + DM groups. In contrast, for the DM Only Without CV Contraindications subpopulation, a lower risk for POE was generally observed in the sibutramine group relative to the placebo group throughout the entire study. These observations are supported by statistical tests of the treatment-by-subgroup interaction at yearly intervals (Table 38).

These findings in the DM Only Without CV Contraindications subpopulation support the previously-discussed difference in the risk profile of the DM Only group compared to the CV Only and CV + DM groups.

Table 38. Cumulative Number (%) of Subjects for POE for DM Only Without CV Contraindications Subpopulation

POE	Placebo N = 896	Sibutramine N = 893	Hazard Ratio	95% CI	*P* value[a]	Interaction *P* value[b]
3 mo	2 (0.2%)	2 (0.2%)	1.042	0.147, 7.407	0.967	
6 mo	6 (0.7%)	4 (0.4%)	0.694	0.196, 2.461	0.572	
12 mo	13 (1.5%)	5 (0.6%)	0.397	0.142, 1.115	0.079	0.008*
24 mo	19 (2.1%)	14 (1.6%)	0.752	0.377, 1.500	0.418	0.138
36 mo	32 (3.6%)	21 (2.4%)	0.661	0.381, 1.147	0.141	0.006*
48 mo	39 (4.4%)	35 (3.9%)	0.906	0.574, 1.431	0.673	0.111
60 mo	47 (5.2%)	42 (4.7%)	0.902	0.595, 1.368	0.628	0.072*
Overall	48 (5.4%)	45 (5.0%)	0.956	0.635, 1.438	0.828	

a. Within–time interval comparisons for difference between treatment groups.

b. Test of treatment-by-subgroup (DM Only Without CV Contraindications subpopulation versus other groups combined) interaction, based on Kaplan-Meier estimates and their standard errors at yearly intervals (Appendix G).

* Statistically significant at the 2-sided 0.10 level.

5.4.7.3 Evaluation of DM Only Subpopulations by Vital Signs and Weight Loss Response and Relationship to POE

For the DM Only subpopulations, the results of the POE analyses comparing the Vital Signs Outliers and Vital Signs Non-Outliers and Weight Loss Responders and Weight Loss Nonresponders for the sibutramine and placebo groups are provided in Table 39 and Table 40, respectively. Data for the "Weight Loss/Vital Signs Conformers" as compared to the "Weight Loss/Vital Signs Nonconformers" are presented in Table 41.

Results for the DM subpopulations were generally consistent with results for the All Subjects population; however, the sample sizes are small and have limited interpretability. The event rates are consistently reduced in the sibutramine Weight Loss/Vital Signs Conformers in comparison to any other group (Table 41).

Table 39. POE Results by Vital Signs Outlier Status for DM Only and DM Only Subpopulations: ITT Population

Analysis	Sibutramine Vital Signs Outlier	Sibutramine Vital Signs Non-Outlier	Placebo Vital Signs Outlier	Placebo Vital Signs Non-Outlier	Sibutramine Vital Signs Non-Outlier vs. Sibutramine Vital Signs Outlier HR (95% CI)	Sibutramine Vital Signs Non-Outlier vs. Placebo Vital Signs Non-Outlier HR (95% CI)
DM Only Group	41/475 (8.6%)	28/676 (4.1%)	21/367 (5.7%)	49/774 (6.3%)	0.482 (0.298, 0.779)	0.664 (0.417, 1.057)
DM Only Without CV Contra-indications	24/364 (6.6%)	21/529 (4.0%)	14/284 (4.9%)	34/612 (5.6%)	0.607 (0.338, 1.092)	0.727 (0.422, 1.253)
DM Only Indicated per US Label	8/151 (5.3%)	8/227 (3.5%)	4/133 (3.0%)	8/257 (3.1%)	0.673 (0.252, 1.796)	1.118 (0.419, 2.979)

Notes: Vital Signs Outliers were defined as subjects with increases above lead-in baseline in SBP or DBP (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment.

The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for gender and age at Lead-in Period Baseline.

Table 40. POE Results by Weight Loss Responders for DM Only and DM Only Subpopulations: ITT Population

Analysis	Sibutramine Nonresponder	Sibutramine Responder	Placebo Nonresponder	Placebo Responder	Sibutramine Responder vs. Sibutramine Nonresponder HR (95% CI)	Sibutramine Responder vs. Placebo Responder HR (95% CI)
DM Only Group	47/787 (6.0%)	22/364 (6.0%)	56/917 (6.1%)	14/224 (6.3%)	1.119 (0.672, 1.863)	0.966 (0.493, 1.891)
DM Only Without CV Contra-indications	34/624 (5.4%)	11/269 (4.1%)	39/719 (5.4%)	9/177 (5.1%)	0.797 (0.403, 1.576)	0.750 (0.311, 1.814)
DM Only Indicated per US Label	14/263 (5.3%)	2/115 (1.7%)	9/315 (2.9%)	3/75 (4.0%)	0.346 (0.077, 1.548)	0.412 (0.069, 2.469)

Notes: The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for gender and age at Lead-in Period Baseline.
Weight Loss Responders were defined as subjects who lost at least 5% of their baseline weight at Month 1 and/or Month 2 of the double-blind Treatment Period.

Table 41. POE Results by Weight Loss/Vital Signs Conformer Status for DM Only and DM Only Subpopulations: ITT Population

Analysis	Sibutramine Weight Loss/Vital Signs Non-conformers	Sibutramine Weight Loss/Vital Signs Conformers	Placebo Weight Loss/Vital Signs Non-conformers	Placebo Weight Loss/Vital Signs Conformers	Sibutramine Weight Loss/Vital Signs Conformers vs. Sibutramine Weight Loss/Vital Signs Nonconformers HR (95% CI)	Sibutramine Weight Loss/Vital Signs Conformers vs. Placebo Weight Loss/Vital Signs Conformers HR (95% CI)
DM Only Group	60/922 (6.5%)	9/229 (3.9%)	61/976 (6.3%)	9/165 (5.5%)	0.655 (0.324, 1.323)	0.773 (0.304, 1.966
DM Only Without CV Contra-indications	40/716 (5.6%)	5/177 (2.8%)	43/764 (5.6%)	5/132 (3.8%)	0.524 (0.207, 1.329)	0.719 (0.208, 2.493)
Indicated per US Label	14/304 (4.6%)	2/74 (2.7%)	10/335 (3.0%)	2/55 (3.6%)	0.641 (0.143, 2.878)	0.596 (0.084, 4.242)

Notes: Weight Loss/Vital Signs Conformers are subjects who were Weight Loss Responders *and* who did not meet criteria for vital signs outliers (i.e., were Vital Signs Non-Outliers)

Weight Loss Responders were defined as subjects who lost at least 5% of their baseline weight at Month 1 and/or Month 2 of the double-blind Treatment Period.

Vital Signs Outliers were defined as subjects with increases above lead-in baseline in SBP or DBP (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment

The hazard ratio is for the treatment group comparison from the Cox proportional hazards model adjusted for gender and age at Lead-in Period Baseline.

5.4.8 Statistical Modeling of SCOUT Results in a Population of Weight Loss/Vital Signs Conformers

In the SCOUT study, subjects continued to receive randomized treatment regardless of whether sufficient weight loss had been achieved, in contrast to instructions in the label. Consequently, the results of SCOUT do not directly apply to the labeled setting.

Therefore, an alternative analysis of the primary endpoint based on estimates of sibutramine event rates that would be expected if sibutramine-treated subjects with insufficient weight loss were discontinued from treatment, as recommended in the label,

is warranted. This analysis was based on the incidence density for events, defined as the ratio of the total number of events to the total duration of follow-up time. Estimated incidence densities for events per subject-year were 490/20,781.60 = 0.0236 for placebo and 561/20,626.26 = 0.0272 for sibutramine, corresponding to an incidence density ratio of 1.154, similar to the hazard ratio of 1.162 from the time-to-event analysis. For this analysis, subjects were divided into 2 groups (Weight Loss Responders and Weight Loss Nonresponders), on the basis of whether they had at least a 5% weight loss from the Lead-in Period baseline at either double-blind Month 1 or 2.

This alternative analysis imputed the number of events for sibutramine Weight Loss Nonresponders, based on the placebo incidence density, as sibutramine-treated subjects would be expected to experience events at the placebo rate after they were withdrawn from sibutramine. This imputation was performed as follows:

- For all placebo-treated subjects and for the sibutramine responders, no imputation was performed; their data were analyzed as reported. Data for sibutramine nonresponders who experienced events (or who were lost to follow-up) prior to a cutoff time of double-blind Month 5 were also included in analysis without imputation. This choice of cutoff time provides an additional 3 months (after treatment should have been discontinued) where events plausibly could be attributed to the exposure to sibutramine. For sibutramine nonresponders without events prior to the cutoff time and who were followed up beyond the cutoff time (N = 3364, 778, 615, and 260 for those who were followed up in the ITT population, the DM Only group, the DM Only Without CV Contraindications subpopulation, and the DM Only Indicated per US Label subpopulation, respectively), imputation was performed, whereby each subject was assigned an "imputed event fraction" (a value between 0 and 1). This event fraction is interpreted as the expected number of events that a subject would have had after discontinuation from sibutramine treatment, if therapy were discontinued as directed by the sibutramine label.
- Using the placebo-treated subjects without events prior to the double-blind Month 5 cutoff time, their subsequent incidence density was calculated. (For

example, for the ITT population, this density was calculated to be 0.0240 events per subject-year.) This value was used to provide the "imputed event fraction" for each sibutramine subject for whom imputation was performed. This event fraction was calculated as the subject's subsequent time of exposure multiplied by the placebo incidence density (0.0240 for ITT). For this purpose, sibutramine exposure was considered to begin at double-blind Month 5 and to end at the subject's last follow-up time in the study. (This is the death date for the subjects who died, and it is the last follow-up time in the study for subjects who had no event or had a nonfatal event with subsequent follow-up).

A Poisson regression analysis to compare incidence densities between treatment groups was then performed using both non-imputed and imputed data from all subjects in both treatment groups, including exposure prior to and after the cutoff time (i.e., beginning at randomization for all subjects. Unless otherwise specified, for subjects for whom imputation was not performed, the end of exposure time was defined as the time of event for subjects with events and as the last follow-up time for subjects without events. For subjects for whom imputation was performed, the end of exposure time was defined as the subject's last follow-up time in the study.

For the ITT population, this analysis resulted in an incidence density ratio of 1.013, substantially reduced from the value of 1.154, which was based on the manner in which sibutramine was used in SCOUT (i.e., without imputation). Corresponding incidence density ratios (with imputation) for the DM Only group, the DM Only Without CV Contraindications subpopulation, and the DM Only Indicated per US Label subpopulation were 0.971, 0.904, and 0.809, respectively (Table 42).

Table 42. Analyses of Incidence Densities Using Poisson Regression with Imputation Based on Weight Loss

	Placebo			Sibutramine			
Analysis Set	Events	Subject Years	ID	Events	Subject Years	ID	IDR
ITT	490	20,782	0.0236	503.646	21,076	0.0239	1.013
DM Only	70	5,520	0.0127	69.287	5,628	0.0123	0.971
DM Only wo CV	48	4,370	0.0110	43.674	4,400	0.0099	0.904
Per Label	12	1,928	0.0062	9.453	1,877	0.0050	0.809

Note: ID = Incidence density (events/subject-year), IDR = Incidence density ratio (sibutramine/placebo), DM Only wo CV = DM Only Without CV Contraindications subpopulation, Per Label = DM Only Indicated per US Label subpopulation

These results support the interpretation that the increased risk of cardiovascular events observed in the sibutramine group relative to that of the placebo group in SCOUT is attributable to subjects with inadequate weight loss at 3 months of therapy remaining on treatment for up to 6 years. The reduction in estimated risk due to the imputation, furthermore, results in a relative risk of less than 1 for the DM Only group, a numerically smaller relative risk for the DM Only Without CV Contraindications subpopulation, and smaller still for the DM Only Indicated per US Label subpopulation, although results must be interpreted with caution for this latter group because of the small sample sizes and very small numbers of events.

Furthermore, a corresponding alternative analysis of the primary endpoint was also performed in order to obtain estimates of sibutramine event rates that would be expected if sibutramine-treated subjects with either insufficient weight loss from baseline (< 5%) or 2 consecutive elevations in DBP, SBP, or pulse rate (changes from baseline of at least 10 mmHg or 10 bpm) were discontinued from treatment. For this analysis, subjects were divided into 2 groups (sibutramine Weight Loss/Vital Signs Conformers or sibutramine Weight Loss/Vital Signs Nonconformers), based on the above criteria.

For the ITT population, this analysis resulted in an incidence density ratio of 0.984, again substantially reduced from the value of 1.154, which was based on the manner in which sibutramine was used in SCOUT (i.e., without imputation). Corresponding incidence density ratios (with imputation) for the DM Only group, the DM Only Without CV Contraindications subpopulation, and the DM Only Indicated per US label subpopulation were 0.905, 0.888, and 0.908, respectively (Table 43).

Table 43. Analyses of Incidence Densities Using Poisson Regression with Imputation Based on Weight Loss/Vital Signs Conformity

Analysis Set	Placebo			Sibutramine			
	Events	Subject Years	ID	Events	Subject Years	ID	IDR
ITT	490	20,782	0.0236	490.616	21,142	0.0232	0.984
DM Only	70	5,520	0.0127	64.654	5,635	0.0115	0.905
DM Only wo CV	48	4,370	0.0110	42.953	4,404	0.0098	0.888
Per Label	12	1,928	0.0062	10.613	1,877	0.0057	0.908

Note: ID = Incidence density (events/subject-year), IDR = Incidence density ratio (sibutramine/placebo), DM Only wo CV = DM Only Without CV Contraindications subpopulation, Per Label = DM Only Indicated per US Label subpopulation.

These results support the interpretation that the increased risk of cardiovascular events observed in the sibutramine group relative to that of the placebo group in SCOUT is attributable to subjects with inadequate weight loss or unacceptable increases in blood pressure or pulse at 3 months of therapy remaining on treatment for up to 6 years. As with the previous results, the estimated risk becomes progressively smaller as the population analyzed has progressively lesser baseline CV risk, with the exception of the labeled group. The results for the DM Only Indicated per US Label subpopulation must be interpreted with caution because of the small sample sizes and very small numbers of events.

These conclusions are supported by the results of numerous sensitivity analyses based on changes in statistical conventions and by similar analyses based on crude event rates rather than on incidence densities.

5.5 SCOUT Conclusions

SCOUT Background

- As a postapproval commitment, CHMP required the conduct of the SCOUT study, a CV outcomes study to evaluate the long-term consequences of sibutramine's effect on pulse and blood pressure.
- An ad hoc CHMP protocol committee required specific study design features to ensure that an adequate CV outcome event rate would be achieved. This was to ensure the feasibility of the study (i.e., that the study would not take too long or require an exceedingly large number of subjects). These requisite design features included the following:
  - Enrollment of older subjects at high risk for CV events (e.g., with a history of MI or stroke).
  - Subject exposure to long-term treatment (up to 6 years), far greater than the standard 1 to 2 years of treatment.
  - The continuation of treatment for all subjects, regardless of whether they experienced weight loss, as opposed to the recommended practice of discontinuing therapy for inadequate weight loss.
  - A 6-week Lead-in Period during which all subjects received sibutramine treatment, even those eventually randomized to the placebo group.
- These design features need to be considered when analyzing the results of SCOUT, and when applying the results of SCOUT to the use of sibutramine in the indicated population. Notably, these features may have served to amplify risk and minimize potential benefit of sibutramine treatment:
  - The enrollment requirements resulted in a SCOUT population at high risk for experiencing a CV event, a population far removed from the indicated patient population;
  - The continued long-term treatment in SCOUT of all subjects, regardless of weight loss, continued to expose subjects to the potential risks of the drug, in the absence of weight loss benefit; and
  - The 6-week Lead-in Period was intended as a safety measure to prevent subjects with significant elevations in pulse or blood pressure from receiving prolonged sibutramine exposure. However, the weight loss

observed in the placebo group was enhanced by Lead-in Period treatment with sibutramine, which likely reduced the observed treatment difference.

- SCOUT was not designed to provide information about the beneficial impact of sibutramine-related weight loss on risk factors associated with obesity, such as improving lipid profiles or glycemic control. Rather, individual subject treatment was optimized with other approved medications intended to treat these comorbid conditions.

SCOUT Results

- SCOUT confirmed that sibutramine treatment promotes clinically relevant weight loss and maintenance of weight loss in a substantial percentage of subjects.
- Mean blood pressure measurements tended to be higher in the sibutramine group as compared with the placebo group, with differences in mean SBP ranging from –0.4 to 1.1 mmHg and in mean DBP from 0.6 to 1.4 mmHg. Mean pulse measurements were higher in the sibutramine group compared with the placebo group, with differences in mean pulse measurements ranging from 2.2 to 3.7 bpm.
- The primary endpoint analysis for SCOUT was a time-to-event analysis of the composite of primary outcome events (POE; nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, and CV death).
- The primary endpoint result demonstrated a 16% increase in the risk of POE in the sibutramine group relative to the placebo group (sibutramine 11.4%, placebo 10.0%; HR = 1.162, 95% CI = 1.029–1.311), which was due to an increase in the risk for nonfatal MI and stroke events.
- No increased risk of death (CV Death [HR = 0.984, 95% CI = 0.831–1.166] or All-Cause Mortality [HR = 1.043, 95% CI = 0.910–1.196]) was observed.
- All SCOUT subjects were categorized into 1 of 3 protocol-specified CV risk groups: 1) those with a history of type 2 diabetes mellitus (DM) with an additional risk factor (DM Only group), 2) those with a history of cardiovascular disease (CV Only group), 3) and those meeting both criteria (CV + DM group).

- Results based on the prespecified CV risk groups showed that the increased risk for nonfatal events with sibutramine was observed in the groups with a known medical history of cardiovascular disease (CV Only and CV + DM groups); however, no increased risk for POE was seen in the group without a history of known cardiovascular disease (that is, the DM Only group) (sibutramine 6.0%, placebo 6.1%; HR = 1.002, 95% CI = 0.718–1.398).

- Because subjects in SCOUT were not managed in accordance with standard clinical practice or the US label (e.g., subjects were treated for an extended period of time, regardless of weight loss), the extrapolation of the results of SCOUT to the on-label population required assessment of not only the prespecified analyses but also of post hoc analyses, which include covariates affected by treatment.
  - In post hoc analyses, subjects with increases in blood pressure (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive study visits during the first 3 months of treatment were classified as "Vital Signs Outliers." "Vital Signs Non-Outliers" did not meet this criterion.
    - Sibutramine Vital Signs Non-Outliers (10.7%) had a lower risk for POE as compared to the sibutramine Vital Signs Outliers (12.7%) (HR = 0.864, 95% CI = 0.729–1.024).
    - No difference in risk for POE was seen between sibutramine and placebo Vital Signs Non-Outliers (sibutramine 10.7%, placebo 10.4%, HR = 1.047, 95% CI = 0.904–1.214).
  - Also in post hoc analyses, subjects with at least 5% weight loss during the first 3 months of treatment were classified as "Weight Loss Responders." "Weight Loss Nonresponders" did not meet these criteria.
    - Sibutramine Weight Loss Responders (9.5%) had a lower risk of POE as compared to sibutramine Weight Loss Nonresponders (12.3%) (HR = 0.808, 95% CI = 0.668–0.979).
  - Subjects with both Weight Loss Response and Vital Signs Non-Outlier status were classified as "Weight Loss/Vital Signs Conformers." "Weight Loss/Vital Signs Nonconformers" did not meet these criteria.

- Sibutramine Weight Loss/Vital Signs Conformers (8.1%) had a lower risk of POE as compared to sibutramine Weight Loss/Vital Signs Nonconformers (12.3%) (HR = 0.673, 95% CI = 0.532–0.853).
- No difference in risk for POE was seen between sibutramine (8.1%) and placebo Weight Loss/Vital Signs Conformers (7.9%) (HR = 1.019, 95% CI = 0.727–1.428).
- Furthermore, although the numbers are small, in the DM Only group, the sibutramine Weight Loss/Vital Signs Conformers (3.9%) had a suggestion of a lower risk of POE than placebo Weight Loss/Vital Signs Conformers (5.5%) (HR = 0.773, 95% CI = 0.304–1.966).

Application of SCOUT Results to the Indicated Population

SCOUT validates the labeled contraindication for patients with a history of cardiovascular disease. On the basis of the findings from SCOUT, current guidance in the US label regarding the need to monitor blood pressure, pulse and weight loss, and advice on when to adjust or discontinue therapy with Meridia should be revised as follows:

- Therapy should not be continued in patients with increases in blood pressure (≥10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive assessments during the first 3 months of treatment.
- Therapy should not be continued in patients who do not achieve at least 5% weight loss response (at 3 months) to sibutramine.

6.0 Cardiovascular Safety of Sibutramine from Non-SCOUT Data Sources

Abbott has utilized multiple sources of safety data to describe the frequency of cardiovascular events in a population aligned with the labeled indication of sibutramine for the treatment of obesity. The sources of information include:

- An integrated analysis of sibutramine clinical trials in obese subjects
- Pharmacovigilance postmarketing surveillance data
- Review of sibutramine published literature
- A recently published observational study of subjects in New Zealand who received sibutramine for the treatment of obesity

6.1 Sibutramine Integrated Clinical Trials (ICT) Analyses

The primary objective of the ICT assessment was to analyze the occurrence of adverse events related to CV outcomes of interest (nonfatal MI and nonfatal stroke) in clinical trial subjects who were obese but without high CV risk, i.e., the population for whom sibutramine use is indicated. Although the SCOUT results did not indicate increased risk with sibutramine for either CV Death or All-Cause Mortality, an additional objective of the ICT Safety Assessment was to evaluate all deaths regardless of cause.

This analysis was performed using an ICT database, which included information from 46 randomized, double-blind, placebo-controlled trials and an additional 22 open-label or non-placebo-controlled studies for the indicated population. This analysis provided safety experience for a total of 20,079 sibutramine-treated subjects.

The selected adverse events evaluated included all serious and non-serious adverse events that may have been potentially consistent with events of MI (SMQs of MI and Other Ischaemic Heart Disease) and stroke (SMQs of Ischaemic Cerebrovascular Conditions and Haemorrhagic Cerebrovascular Conditions). The results of this analysis are summarized in Table 44.

Table 44. SMQs Related to Nonfatal CV Outcome Events: Placebo-Controlled and All Sibutramine On-Label Analysis Sets

	Placebo-Controlled Analysis Set		
SMQ	**Placebo N = 3491**	**Sibutramine N = 5812**	**All Sibutramine N = 20079**
Myocardial Infarction			
No. of Subjects (%)	3 (< 0.1)	2 (< 0.1)	5 (< 0.1)
Events	3	3	6
E/100PY	0.119	0.076	0.060
HR (95% CI)	0.463 (0.077, 2.781)		NA
Other Ischaemic Heart Disease			
No. of Subjects (%)	10 (0.3)	11 (0.2)	25 (0.1)
Events	11	11	26
E/100PY	0.437	0.279	0.259
HR (95% CI)	0.772 (0.320, 1.865)		NA
Ischaemic Cerebrovascular Conditions			
No. of Subjects (%)	6 (0.2)	13 (0.2)	20 (< 0.1)
Events	6	13	21
E/100PY	0.238	0.329	0.209
HR (95% CI)	1.402 (0.522, 3.763)		NA
Haemorrhagic Cerebrovascular Conditions			
No. of Subjects (%)	3 (< 0.1)	5 (< 0.1)	8 (< 0.1)
Events	3	5	9
E/100PY	0.119	0.127	0.090
HR (95% CI)	0.945 (0.218, 4.094)		NA

E/100PY = events per 100 person-years; HR = hazard ratio; CI = confidence interval; SMQ = standardized MedDRA query

Note: HR is for treatment effect by Cox proportional hazards modeling.

In the placebo-controlled analysis set, incidence rates for nonfatal myocardial infarction were < 0.1% for both sibutramine and placebo-treated subjects. The hazard ratio was 0.463 (95% CI = 0.077–2.781). Incidence rates from the analysis of nonfatal events from the "other ischemic heart disease" SMQ (e.g., reports of angina pectoris or coronary

artery disease) were 0.2% for the sibutramine group and 0.3% for the placebo group, with a hazard ratio of 0.772 (95% CI = 0.320–1.865).

Incidence rates for nonfatal ischemic cerebrovascular events were 0.2% for both sibutramine- and placebo-treated subjects. While the point estimate for the hazard ratio for ischemic cerebrovascular conditions was 1.4, the difference between the sibutramine and placebo groups did not reach statistical significance and was accompanied by a wide confidence interval (95% CI = 0.522–3.763).

Incidence rates for nonfatal hemorrhagic cerebrovascular events were < 0.1% for both sibutramine and placebo-treated subjects. The hazard ratio was 0.945 (95% CI = 0.218–4.094). Of note, the preferred terms of cerebrovascular accident and cerebrovascular disorder in the SMQ of Haemorrhagic Cerebrovascular Conditions overlap those in the SMQ of Ischaemic Cerebrovascular Conditions. Therefore, there is only 1 unique case (subarachnoid haemorrhage) for the sibutramine group presented in this SMQ, while the remaining 7 events overlap with the Ischaemic Cerebrovascular Conditions SMQ.

In addition to nonfatal adverse events identified by analysis of the 4 SMQs for the evaluation of nonfatal stroke and MI, an analysis of all deaths from treatment-emergent adverse events regardless of cause was conducted; the results are summarized in Table 45.

Table 45. Treatment-Emergent Adverse Events of Interest Resulting in Death Among Subjects in the Placebo-Controlled and All Sibutramine On-Label Analysis Sets

	Number (%) of Subjects		
	Placebo-Controlled Analysis Set		All
MedDRA Preferred Term	Placebo N = 3491	Sibutramine N = 5812	Sibutramine N = 20079
Acute myocardial infarction	0	1 (< 0.1)	1 (< 0.1)
Coronary artery disease	0	1 (< 0.1)	1 (< 0.1)
Myocardial infarction	1 (< 0.1)	0	1 (< 0.1)

In the placebo-controlled analysis set, All-Cause Mortality rates were low for both sibutramine-treated subjects (4 of 5,812; < 0.1%) and placebo-treated subjects (4 of 3,491; 0.1%). Deaths from cardiovascular causes were reported for 2 sibutramine-treated subjects (acute myocardial infarction and complications of coronary artery disease) and 1 placebo-treated subject (myocardial infarction).

6.2 Literature-Based Review of Cardiovascular Events

Abbott conducted a literature-based review of cardiovascular events reported in published sibutramine clinical trials in obese subjects through June 2010. The literature review was limited to those clinical trials that evaluated sibutramine therapy for the treatment of weight loss or weight loss maintenance. This included a total of 60 unique trials, including 34 placebo-controlled trials and 26 open-label or active comparator trials. Of note, these clinical trials were not company sponsored or did not include subject level data and, therefore, do not overlap with trials included in the ICT analysis. Major cardiovascular events were defined as coronary heart disease (CHD) death, nonfatal MI, or stroke. Results from this review were as follows:

- In a total of 34 placebo-controlled trials for weight loss, 2,312 subjects received sibutramine in a dose range of 10 to 20 mg per day, and 1,856 subjects received placebo and 260 subjects received an active comparator.
- None of the 34 trials reported a major cardiovascular event, cardiovascular mortality, or All-Cause Mortality. Across all placebo-controlled trials, cardiovascular events were reported for only 5 subjects.
    - 3 events were reported for sibutramine-treated subjects, including cardiac arrhythmia that resolved within 24 hours without intervention, non-cardiac chest pain, and ventricular extrasystoles.
    - 2 events were reported for non–sibutramine-treated subjects, including 1 event of atrial fibrillation for placebo and 1 event of ventricular extrasystoles for active-control (orlistat).

- None of the open-label (N = 17) or active-controlled (N = 9) studies included in this literature review identified any major cardiovascular events, cardiovascular mortality, or All-Cause Mortality.

6.3 Postmarketing Experience

The Abbott global postmarketing surveillance safety database contains reports of adverse events including spontaneously reported adverse events received directly from health care professionals and from the general public. Additional sources for adverse events include reports from the literature and adverse event reports from clinical trials or postmarketing surveillance studies. The limitations of postmarketing data are well recognized and include underreporting, bias as to which cases are selected for reporting, variable quality of the information in any particular case and lack of precise numbers of subjects who undergo treatment.

There has been extensive postmarketing global experience with sibutramine including subject exposure estimated at over 6 million PTY; however, the above noted factors complicate the ability of postmarketing data to estimate a true incidence of any adverse event or to establish a definitive cause-effect relationship between the drug and an adverse event.

To review the reported adverse events with sibutramine in the "real-world setting," the Abbott safety database was searched for sibutramine cases entered from the first regulatory approval of sibutramine (12 November 1997) through 20 May 2010, excluding cases derived from clinical trials. There were 3 areas of concentrated review: fatalities, myocardial infarction events, and cerebrovascular events. Assessment of individual spontaneous reports of cardiac or stroke events with sibutramine use is significantly confounded by the underlying obesity and comorbidities including an increase in cardiovascular and cerebrovascular events.

Epidemiologic data from scientific literature is presented as a means of reference for estimated reporting rates from the sibutramine postmarketing safety database. Obesity has been associated with both an increased risk of mortality and an increased risk of

morbid conditions that directly elevate the risk of mortality. Epidemiologic data from the US-based Framingham study were considered to provide the most appropriate context for sibutramine postmarketing reports, as event rates were presented in BMI subgroups for All-Cause Mortality as well as for specific cardiovascular events. Moreover, the Framingham study provided exposure data, allowing for calculation of event rates in person-years.[54]

Notwithstanding the limitations of the data, the following results are noted:

Overall Fatalities Including Myocardial Infarction and Cerebrovascular Events

The reporting rate for overall fatalities from any cause was 0.0029/100 PTY (179 reports). Many of the reports contain confounding factors and medical conditions associated with death (e.g., malignancies, accidents, serious infections).

- For context, epidemiologic data in an obese population derived from the Framingham Heart Study estimate a rate of all-cause mortality ranging from 0.12 to 0.22 per 100 person-years (based upon variable BMI and gender).

The reporting rates for fatalities from myocardial infarction or cerebrovascular events from the sibutramine postmarketing database were 0.00022/100 PTY (14 reports) and 0.00014/100 PTY (9 reports), respectively.

- For context, in the Framingham Heart Study the rate of cerebrovascular disease/cardiovascular mortality ranged from 0.03 to 0.07 per 100 person-years (based upon variable BMI and gender).

Nonfatal Myocardial Infarction and Cerebrovascular Events

The report rate for nonfatal myocardial infarction was 0.0012/100 PTY (72 reports).

- In the Framingham Heart Study, the rate of myocardial infarction ranged from 0.04 to 0.17 per 100 person-years based upon variable BMI and gender.

- Analysis of the individual reports demonstrated most cases presented confounding factors or had an alternative etiology for the event of nonfatal myocardial infarction.

The reporting rate for nonfatal cerebrovascular accidents and TIA was 0.0027/100 PTY (169 reports).

- For context, the rate of cerebrovascular disease events in an obese population derived from the Framingham Heart Study ranged from 0.06 to 0.1 per 100 person-years based upon variable BMI and gender.
- Analysis of the individual cases demonstrated that many cases present with alternative etiologies and complicating conditions, reflecting the known comorbidities of obesity, that some cases indicated off-label use, and that additional cases present insufficient information to allow a medical assessment.

6.4 Prospective Observational Cohort Study: Fatal and Nonfatal Cardiovascular Events in a General Population Prescribed Sibutramine in New Zealand

The Intensive Medicines Monitoring Programme of New Zealand conducted a prospective observational cohort study in the setting of "real life" use of sibutramine.[55] This included all subjects in New Zealand who were dispensed a prescription for sibutramine in a 3-year period with a validated cohort of 15,686 subjects (5,431 treatment-years). The study included record linkage for fatal events. Results from this observational study confirm the low event rates observed in the Abbott ICT analyses:

- Death from all causes was observed at a rate of 0.13 (95% CI = 0.05–0.27) per 100 treatment-years.
- Death from a cardiovascular event was observed at a rate of 0.07 (95% CI = 0.02–0.19) per 100 treatment-years.
    - Three of 4 deaths from cardiovascular causes (2 cases of stroke and one myocardial infarction) may have been related to sibutramine according to the authors.

- However, the presence of confounding factors (including a history of metastatic pancreatic carcinoma in 1 subject with CVA and hypertension in the second case and type 2 diabetes mellitus, hypertension, and endstage renal disease in the subject with acute MI) complicates this assessment.

- Nonfatal cerebrovascular and myocardial events were calculated for 3 denominator populations in the sibutramine cohort based on the extent of follow-up and response to questionnaires.
  - Nonfatal "cerebrovascular accidents" ranged from 0.19 to 0.50 per 1,000 subjects (approximately 0.05 to 0.14 events per 100 treatment-years).
  - Nonfatal "myocardial ischemia" ranged from 1.08 to 3.52 per 1,000 subjects (approximately 0.31 to 1.02 events per 100 treatment-years).
  - Nonfatal "myocardial infarction" was observed in a single case in the validated cohort denominator of 15,686 subjects (0.06 per 1,000 subjects) with no data for the other 2 denominator populations.

6.5 Summary

Overall, the data indicate that use of sibutramine in the on-label or "real-world" population is associated with a low absolute rate of CV events. Additionally the ICT analysis suggests that there is no increase in risk with sibutramine treatment compared to placebo for CV events or death.

7.0 Rates of Off-Label Use of Sibutramine in the United States

Introduction

To characterize prescribing of Meridia (sibutramine hydrochloride monohydrate) in a "real-world" population, Abbott commissioned GE Healthcare to conduct an epidemiology study to investigate on- and off-label use status of patients on Meridia at the time of their first prescription.

The criteria for off-label use that was applied to this study was based on the US label for Meridia that was implemented in January 2010; this offers the most conservative assessment (i.e., provides the highest estimate of off-label use), because additional restrictions on the use of Meridia were added during the marketing history of the product.

Methodology

Data from a large US electronic medical record database (GE Healthcare) identified 7,919 new users of sibutramine for the years 1997 to 2010 who met the following criteria:

- Patients who had at least 1 year of data in the electronic medical record.
- Patients who had a recorded blood pressure, heart rate, and BMI (or weight and height) within the 90 days before the first prescription of sibutramine were selected for analysis.

Patients were considered "on-label" if they complied with the approved indication and had none of the conditions described in the contraindications, warnings or precautions for Meridia, as specified in the Meridia US label implemented in January 2010. Specifically, patients had to meet the following criteria:

- Patient has a BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other comorbidities (dyslipidemia, diabetes, controlled hypertension).
- Patient does not currently have, or have a history of, any of the following: coronary artery disease (e.g., angina, history of myocardial infarction),

congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia, or cerebrovascular disease (stroke or transient ischemic attack).

- Patient does not have inadequately controlled hypertension (> 145/90 mmHg).
- Patient is not older than 65 years of age or younger than 16 years of age.
- Patient is not currently taking/has not been taking monoamine oxidase inhibitors (MAOIs) during the past 2 weeks.
- Patient is not currently taking /has not been taking other centrally acting drugs for weight reduction.
- Patient does not have a major eating disorder such as anorexia nervosa or bulimia nervosa.

Results

A total of 7,919 new users of sibutramine were identified from the database for the years 1997 to 2010, and included in this study. The key findings of the study are presented in Table 46.

Table 46. Summary of Reasons for Patient Off-Label Use Status at the Time of the First Prescription of Sibutramine in the US

Off-Label Indication or Condition	Number (%) N = 7919
Indication	
Off-label BMI	1368 (17.3)
BMI < 27kg/m^2	480 (6.1)
BMI ≥ 27 to 30 kg/m^2 without the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension)	888 (11.2)
Contraindications/Warnings/Precautions	
History of coronary artery disease (e.g., angina, history of MI, CHF, tachycardia, peripheral arterial occlusive disease, arrhythmia, stroke, or TIA)	207 (2.6)
Inadequately controlled hypertension	65 (0.8)
Age < 16 years or > 65 years	548 (6.9)
Other off-label medical conditions (e.g., eating disorders, organic causes of obesity, severe hepatic or renal impairment)	118 (1.5)
Off-label medications (SSRI,SNRI, phentermine)	1668 (21.1)
Total number of unique patients with any off-label indication or condition	3292 (41.6)

In summary, the analysis showed the following for patients who were prescribed Meridia:

- 17.3% of patients had an off-label BMI. Of these, 11.2% had a BMI of 27 kg/m^2 or greater without other risk factors, and 6.1% had BMI of less than 27 kg/m^2.
- Off-label age accounted for 6.9% of the patients.
- Use of off-label medications accounted for 21.1% of the patients.
- Importantly, only 2.6% of the patients who were prescribed Meridia had a preexisting cardiovascular condition, and only 0.8% had inadequately controlled blood pressure.

Conclusions

This study of US patients prescribed Meridia showed that very few patients (approximately 3%) had a preexisting cardiovascular condition or inadequately controlled blood pressure in this retrospective database study of Meridia use. These data suggest that prescribing physicians understand the cardiovascular restrictions of use with Meridia.

Most of the "off-label use" was due to prescribing of off-label concomitant medication, which is not a contraindication, but rather a precaution is advised. A number of patients were noted to have a BMI lower than that specified in the approved indication, although the majority would be considered overweight. Off-label use was also observed in patients over 65 years of age; it should be noted that this age group was not contraindicated prior to January 2010.

8.0 Benefit/Risk Profile of Sibutramine

Obesity is recognized as a serious medical condition of epidemic proportions and is associated with significant morbidity and mortality.[2] The World Health Organization projects that, by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese.

Clinical studies and epidemiological evaluations have suggested that moderate weight loss (approximately 5% to 10% reduction from baseline body weight) reduces total mortality and premature death from cardiovascular disease and diabetes in diabetic subjects[16] and reduces the risk of developing type 2 diabetes,[17,18] hypertension[19,20] and obstructive sleep apnea.[21] In addition, weight reduction has been shown to lower blood pressure,[22,23] improve insulin sensitivity and glycemic control,[24,25] and improve lipid parameters.[26]

At the time of approval of the original NDA for Meridia, the efficacy of sibutramine as a weight loss agent was demonstrated in accordance with the FDA 1996 Draft Guidance for the Clinical Evaluation of Weight-Control Drugs.[37] Sibutramine continues to meet the FDA's weight loss criteria as defined in the 1996 Guidance, and the subsequent 2007 revision.[1] Analyses of extensive clinical trial data since the time of the initial NDA approval confirm the findings from the registration studies, and further underscore the weight loss efficacy of sibutramine.

Compared to placebo, sibutramine treatment results in:

- Greater mean absolute and percentage weight loss (4.08 kg and 4.28% difference from placebo at 12 months)
- Greater proportions of subjects achieving ≥ 5%, ≥ 10%, and ≥ 15% weight loss (26.5%, 14.7%, and 7.6% difference from placebo at 12 months)

In general, 3 months of treatment with sibutramine is adequate to identify those who respond to treatment (i.e., achieve at least 5% weight loss). Continued use of sibutramine in weight loss responders results in maintenance of achieved weight loss. Sibutramine

use is also associated with improvements in obesity-related risk factors (TG and HDL-C) to an extent that is commensurate with the degree of weight loss achieved.

The impact of sibutramine on a range of weight-related comorbidities was investigated in post-registration clinical studies. Results suggested that weight reduction with sibutramine improved sleep-disordered breathing and symptoms in subjects with obstructive sleep apnea,[41] improved the metabolic and reproductive abnormalities that characterize PCOS in women of reproductive age,[42,43] and improved health-related quality of life.[44]

The safety profile of sibutramine is well characterized. As described in the US label for Meridia, sibutramine has been associated with mean increases as compared to placebo in SBP and DBP of 1 to 3 mmHg and in pulse of 4 to 5 bpm. Importantly, most patients who experience sustained increases in blood pressure and pulse on sibutramine can be identified early (within the initial 3 months) and discontinued from treatment. Additionally, the use of sibutramine is contraindicated in patients with a history of cardiovascular disease.

A review of data from both on-label clinical trials and worldwide postmarketing safety indicates a very low absolute rate of cardiovascular outcome events in the target population. Also, a retrospective database review of sibutramine use indicates that off label use in patients with a history of cardiovascular disease is infrequent (approximately 3%).

Furthermore, although sibutramine is a centrally-acting agent, it has not been associated with significant CNS adverse effects.

Benefit/Risk Profile – The Impact of SCOUT

The primary endpoint results of SCOUT demonstrated a 16% increase in risk for POE in the sibutramine group relative to the placebo group, which was due to an increase in the risk for nonfatal MI and stroke events. No increased risk of death (CV Death or All-Cause Mortality) was observed.

SCOUT, however, was conducted in patients with a history of cardiovascular disease, at high risk for cardiovascular events, who were treated for an extended period of time, regardless of weight loss. These design features require consideration of the differences between how patients were selected and managed in SCOUT and how they are selected and managed per standard clinical practice and in accordance with the US label.

Analyses from SCOUT show that the risk of POE was not increased in the sibutramine-treated subjects who would have met criteria for appropriate use consistent with clinical practice and product labeling. Specifically, the results confirm the appropriateness of the label, which contraindicates the use of sibutramine in patients with a known history of cardiovascular disease. Furthermore, even in the high CV risk population, when sibutramine is used appropriately (in those who do not meet criteria for Vital Signs Outlier status by 3 months and who are Weight Loss Responders by 3 months), there is no increased risk for CV outcome events with long-term sibutramine treatment.

The results of SCOUT do not exclude the possibility that benefit based on CV outcome events might be observed if patients with no history of cardiovascular disease were to be treated for an extended period under appropriate conditions of use.

On the basis of the registration program and a review of sibutramine clinical trials, a 3-month course of sibutramine, to determine who should continue long-term treatment, has a minimal risk of cardiovascular events in the indicated population. Moreover, even in the high-CV-risk population enrolled in SCOUT, 3 months of exposure to sibutramine was associated with a low rate of outcome events.

In summary, the totality of data for sibutramine continues to support its effectiveness as a weight loss agent in an appropriate patient population. SCOUT validates the labeled contraindication for patients with a history of cardiovascular disease. On the basis of the findings from SCOUT, current guidance in the US label regarding the need to monitor blood pressure, pulse and weight loss, and advice on when to adjust or discontinue therapy with Meridia should be revised as follows:

- Therapy should not be continued in patients with increases in blood pressure (≥ 10 mmHg) or pulse (≥ 10 bpm) on 2 consecutive assessments during the first 3 months of treatment.
- Therapy should not be continued in patients who do not achieve at least 5% weight loss response (at 3 months) to sibutramine.

Abbott proposes to provide additional advice on monitoring and discontinuation of therapy based on blood pressure, pulse and weight loss parameters as a boxed warning in the US label for Meridia. Abbott is also proposing a number of risk mitigation strategies to better ensure appropriate use of sibutramine. In addition to the recently approved Medication Guide for Meridia, Abbott also proposes to implement a Communication Plan with specific monitoring and screening tools, to educate prescribers and patients of the appropriate use of Meridia and the potential risks of therapy. Abbott plans to evaluate the effectiveness of these educational programs as part of the required assessments for the Risk Evaluation and Mitigation Strategy. The proposed risk mitigation activities are described in Appendix H.

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Appendix A. United States Package Insert for Meridia®

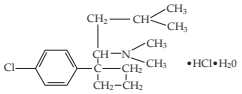
MERIDIA®

(sibutramine hydrochloride monohydrate) Capsules

DESCRIPTION

MERIDIA® (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (-) enantiomers of cyclobutanemethanamine,1-(4-chlorophenyl)-N,N-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$. Its molecular weight is 334.33.

The structural formula is shown below:



Sibutramine hydrochloride monohydrate is a white to cream crystalline powder with a solubility of 2.9 mg/mL in pH 5.2 water. Its octanol: water partition coefficient is 30.9 at pH 5.0.

Each MERIDIA capsule contains 5 mg, 10 mg, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

CLINICAL PHARMACOLOGY

Mode of Action

Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Sibutramine and its major pharmacologically active metabolites (M_1 and M_2) do not act via release of monoamines.

Pharmacodynamics

Sibutramine exerts its pharmacological actions predominantly via its secondary (M_1) and primary (M_2) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5- hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vivo*, but not *in vitro*. However, metabolites M_1 and M_2 inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M_1 and M_2 also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

Potencies of Sibutramine, M_1 and M_2 as *In Vitro* Inhibitors of Monoamine Reuptake in Human Brain Potency to Inhibit Monoamine Reuptake (K_i; nM)

	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M_1	15	20	49
M_2	20	15	45

A study using plasma samples taken from sibutramine-treated volunteers showed monoamine reuptake inhibition of norepinephrine > serotonin > dopamine; maximum inhibitions were norepinephrine = 73%, serotonin = 54% and dopamine = 16%.

Sibutramine and its metabolites (M_1 and M_2) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M_1 and M_2 exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M_1 and M_2 have low affinity for serotonin (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), norepinephrine (β, β_1, β_3, α_1 and α_2), dopamine (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

Pharmacokinetics

Absorption

Sibutramine is rapidly absorbed from the GI tract (T_{max} of 1.2 hours) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 h) to form the pharmacologically active mono- and di-desmethyl metabolites M_1 and M_2. Peak plasma concentrations of M_1 and M_2 are reached within 3 to 4 hours. On the basis of mass balance studies, on average, at least 77% of a single oral dose of sibutramine is absorbed. The absolute bioavailability of sibutramine has not been determined.

Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. *In vitro*, sibutramine, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450 ($3A_3$) isoenzyme, to desmethyl metabolites, M_1 and M_2. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M_5 and M_6. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%).

M_1 and M_2 plasma concentrations reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of M_1 and M_2, 14 and 16 hours, respectively, were unchanged following repeated dosing.

Excretion

Approximately 85% (range 68-95%) of a single orally administered radiolabeled dose was excreted in urine and feces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were M_5 and M_6; unchanged sibutramine, M_1, and M_2 were not detected. The primary route of excretion for M_1 and M_2 is hepatic metabolism and for M_5 and M_6 is renal excretion.

Summary of Pharmacokinetic Parameters

Mean (% CV) and 95% Confidence Intervals of Pharmacokinetic Parameters (Dose = 15 mg)

Study Population	C_{max} (ng/mL)	T_{max} (h)	AUC† (ng*h/mL)	T½ (h)
Metabolite M_1				
Target Population:				
Obese Subjects	4.0 (42)	3.6 (28)	25.5 (63)	--
(n=18)	3.2 - 4.8	3.1 - 4.1	18.1 - 32.9	
Special Population:				
Moderate Hepatic	2.2 (36)	3.3 (33)	18.7 (65)	--
Impairment (n=12)	1.8 - 2.7	2.7 - 3.9	11.9 - 25.5	
Metabolite M_2				
Target Population:				
Obese Subjects	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
(n=18)	5.6 - 7.2	3.2 - 3.8	81.2 - 103	12.5 - 21.8
Special Population:				
Moderate Hepatic	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
Impairment (n=12)	3.4 - 5.2	3.1 - 4.5	76.9 - 104	18.9 - 26.5

† Calculated only up to 24 hr for M_1.

Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M_1 and M_2 concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately three hours. However, the AUCs of M_1 and M_2 were not significantly altered.

Special Populations

Geriatric: Plasma concentrations of M_1 and M_2 were similar between elderly (ages 61 to 77 yr) and young (ages 19 to 30 yr) subjects following a single 15-mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M_5 and M_6 were higher in the elderly; these differences are not likely to be of clinical significance. Sibutramine is contraindicated in patients over 65 years of age (see **CONTRAINDICATIONS**).

Pediatric: The safety and effectiveness of sibutramine in pediatric patients under 16 years old have not been established.

Gender: Pooled pharmacokinetic parameters from 54 young, healthy volunteers (37 males and 17 females) receiving a 15-mg oral dose of sibutramine showed the mean C_{max} and AUC of M_1 and M_2 to be slightly (≤ 19% and ≤ 36%, respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients

from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see **DOSAGE AND ADMINISTRATION**).

Race: The relationship between race and steady-state trough M_1 and M_2 plasma concentrations was examined in a clinical trial in obese patients. A trend towards higher concentrations in Black patients over Caucasian patients was noted for M_1 and M_2. However, these differences are not considered to be of clinical significance.

Renal Insufficiency: The disposition of sibutramine metabolites (M_1, M_2, M_5 and M_6) following a single oral dose of sibutramine was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

In patients with moderate and severe renal impairment, the AUC values of the active metabolite M_1 were 24 to 46% higher and the AUC values of M_2 were similar as compared to healthy subjects. Cross-study comparison showed that the patients with end - stage renal disease on dialysis had similar AUC values of M_1 but approximately half of the AUC values of M_2 measured in healthy subjects (CLcr $\geq$ 80 mL/min). The AUC values of inactive metabolites M_5 and M_6 increased 2 - 3 fold (range 1 - to 7 - fold) in patients with moderate impairment (30 mL/min < CLcr=60 mL/min) and 8 - 11 fold (range 5 - to 15 - fold) in patients with severe impairment (CLcr $\leq$ 30 mL/min) as compared to healthy subjects. Cross-study comparison showed that the AUC values of M_5 and M_6 increased 22 - 33 fold in patients with end - stage renal disease on dialysis as compared to healthy subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of M_5 and M_6 during the hemodialysis process, while M_1 and M_2 were not measurable in the dialysate.

Sibutramine should not be used in patients with severe renal impairment, including those with end-stage renal disease on dialysis.

Hepatic Insufficiency: In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M_1 and M_2 were increased by 24% compared to healthy subjects while M_5 and M_6 plasma concentrations were unchanged. The observed differences in M_1 and M_2 concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Sibutramine should not be used in patients with severe hepatic dysfunction.

Drug-Drug Interactions

In vitro studies indicated that the cytochrome P450 ($3A_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Phase 1 clinical trials were conducted to assess the interactions of sibutramine with drugs that are substrates and/or inhibitors of various cytochrome P450 isozymes. The potential for studied interactions is described below.

Ketoconazole: Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.

Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.

Cimetidine: Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%).

Simvastatin: Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 27 healthy volunteers after the administration of simvastatin 20 mg once daily in the evening and sibutramine 15 mg once daily in the morning for 7 days. Simvastatin had no significant effect on plasma C_{max} and AUC of M_2 or M_1 and M_2 combined. The C_{max} (16%) and AUC (12%) of M_1 were slightly decreased. Simvastatin slightly decreased sibutramine C_{max} (14%) and AUC (21%). Sibutramine increased the AUC (7%) of the pharmacologically active moiety, simvastatin acid and reduced the C_{max} (25%) and AUC (15%) of inactive simvastatin.

Omeprazole: Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 26 healthy volunteers after the co-administration of omeprazole 20 mg once daily and sibutramine 15 mg once daily for 7 days. Omeprazole slightly increased plasma C_{max} and AUC of M_1 and M_2 combined (approximately 15%). M_2 C_{max} and AUC were not significantly affected whereas M_1 C_{max} (30%) and AUC (40%) were modestly increased. Plasma C_{max} (57%) and AUC (67%) of unchanged sibutramine were moderately increased. Sibutramine had no significant effect on omeprazole pharmacokinetics.

Olanzapine: Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 24 healthy volunteers after the co-administration of sibutramine 15 mg once daily with olanzapine 5 mg twice daily for 3 days and 10 mg once daily thereafter for 7 days. Olanzapine had no significant effect on plasma C_{max} and AUC of M_2 and M_1 and M_2 combined, or the AUC of M_1. Olanzapine slightly increased M_1 C_{max} (19%), and moderately increased sibutramine C_{max} (47%) and AUC (63%). Sibutramine had no significant effect on olanzapine pharmacokinetics.

Lorazepam: Steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 after sibutramine 15 mg once daily for 11 days were compared in 25 healthy volunteers in the presence or absence of lorazepam 2 mg twice daily for 3 days plus one morning dose. Lorazepam had no significant effect on the pharmacokinetics of sibutramine metabolites M_1 and M_2. Sibutramine had no significant effect on lorazepam pharmacokinetics.

Drugs Highly Bound to Plasma Proteins: Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

CLINICAL STUDIES

Observational epidemiologic studies have established a relationship between obesity and the risks for cardiovascular disease, non-insulin dependent diabetes mellitus (NIDDM), certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for some patients with chronic obesity who may also be at risk for other diseases.

The long-term effects of sibutramine on the morbidity and mortality associated with obesity have not been established. Weight loss was examined in 11 double-blind, placebo-controlled obesity trials (BMI range across all studies 27-43) with study durations of 12 to 52 weeks and doses ranging from 1 to 30 mg once daily. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5 to 20 mg once daily. In two 12-month studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of placebo-subtracted weight loss achieved on sibutramine was consistent across studies.

Analysis of the data in three long-term (≥ 6 months) obesity trials indicates that patients who lose at least 4 pounds in the first 4 weeks of therapy with a given dose of sibutramine are most likely to achieve significant long-term weight loss on that dose of sibutramine. Approximately 60% of such patients went on to achieve a placebo-subtracted weight loss of ≥ 5% of their initial body weight by month 6. Conversely, of those patients on a given dose of sibutramine who did not lose at least 4 pounds in the first 4 weeks of therapy, approximately 80% did not go on to achieve a placebo-subtracted weight loss of ≥ 5% of their initial body weight on that dose by month 6.

Significant dose-related reductions in waist circumference, an indicator of intra-abdominal fat, have also been observed over 6 and 12 months in placebo-controlled clinical trials. In a 12-week placebo-controlled study of non-insulin dependent diabetes mellitus patients randomized to placebo or 15 mg per day of sibutramine, Dual Energy X-Ray Absorptiometry (DEXA) assessment of changes in body composition showed that total body fat mass decreased by 1.8 kg in the sibutramine group versus 0.2 kg in the placebo group ($p < 0.001$). Similarly, truncal (android) fat mass decreased by 0.6 kg in the sibutramine group versus 0.1 kg in the placebo group ($p < 0.01$). The changes in lean mass, fasting blood sugar, and HbA_1 were not statistically significantly different between the two groups.

Eleven double-blind, placebo-controlled obesity trials with study durations of 12 to 52 weeks have provided evidence that sibutramine does not adversely affect glycemia, serum lipid profiles, or serum uric acid in obese patients. Treatment with sibutramine (5 to 20 mg once daily) is associated with mean increases in blood pressure of 1 to 3 mm Hg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These findings are similar in normotensives and in patients with hypertension controlled with medication. Those patients who lose significant (≥ 5% weight loss) amounts of weight on sibutramine tend to have smaller increases in blood pressure and pulse rate (see **WARNINGS**).

In Study 1, a 6-month, double-blind, placebo-controlled study in obese patients, Study 2, a 1-year, double-blind, placebo-controlled study in obese patients, and Study 3, a 1-year, double-blind, placebo-controlled study in obese patients who lost at least 6 kg on a 4-week very low calorie diet (VLCD), sibutramine produced significant reductions in weight, as shown below. In the two 1-year studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months.

Mean Weight Loss (lbs) in the Six-Month and One-Year Trials

	Sibutramine (mg)				
Study/Patient Group	**Placebo (n)**	**5 (n)**	**10 (n)**	**15 (n)**	**20 (n)**
Study 1					
All patients*	2.0 (142)	6.6 (148)	9.7 (148)	12.1 (150)	13.6 (145)
Completers**	2.9 (84)	8.1 (103)	12.1 (95)	15.4 (94)	18.0 (89)
Early responders***	8.5 (17)	13.0 (60)	16.0 (64)	18.2 (73)	20.1 (76)
Study 2					
All patients*	3.5 (157)		9.8 (154)	14.0 (152)	
Completers**	4.8 (76)		13.6 (80)	15.2 (93)	
Early responders***	10.7 (24)		18.2 (57)	18.8 (76)	
Study 3****					
All patients*	15.2 (78)		28.4 (81)		
Completers**	16.7 (48)		29.7 (60)		
Early responders***	21.5 (22)		33.0 (46)		

* Data for all patients who received study drug and who had any post-baseline measurement (last observation carried forward analysis).

** Data for patients who completed the entire 6-month (Study 1) or one-year period of dosing and have data recorded for the month 6 (Study 1) or month 12 visit.

*** Data for patients who lost at least 4 lbs in the first 4 weeks of treatment and completed the study.

**** Weight loss data shown describe changes in weight from the pre-VLCD; mean weight loss during the 4-week VLCD was 16.9 lbs for sibutramine and 16.3 lbs for placebo.

Maintenance of weight loss with sibutramine was examined in a 2-year, double-blind, placebo-controlled trial. After a 6-month run-in phase in which all patients received sibutramine 10 mg (mean weight loss, 26 lbs.), patients were randomized to sibutramine (10 to 20 mg, 352 patients) or placebo (115 patients). The mean weight loss from initial body weight to endpoint was 21 lbs. and 12 lbs. for sibutramine and placebo patients, respectively. A statistically significantly ($p < 0.001$) greater proportion of sibutramine treated patients, 75%, 62%, and 43%, maintained at least 80% of their initial weight loss at 12, 18, and 24 months, respectively, compared with the placebo group (38%, 23%, and 16%). Also 67%, 37%, 17%, and 9% of sibutramine treated patients compared with 49%, 19%, 5%, and 3% of placebo patients lost ≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%, respectively, of their initial body weight at endpoint. From endpoint to the post-study follow-up visit (about 1 month), weight regain was approximately 4 lbs for the sibutramine patients and approximately 2 lbs for the placebo patients.

Sibutramine induced weight loss has been accompanied by beneficial changes in serum lipids that are similar to those seen with nonpharmacologically-mediated weight loss. A combined, weighted analysis of the changes in serum lipids in 11 placebo-controlled obesity studies ranging in length from 12 to 52 weeks is shown below for the last observation carried forward (LOCF) analysis.

Combined Analysis (11 Studies) of Changes in Serum Lipids - LOCF

Category	**TG % (n)**	**CHOL % (n)**	**LDL-C % (n)**	**HDL-C % (n)**
All Placebo	0.53 (475)	-1.53 (475)	-0.09 (233)	-0.56 (248)
< 5% Weight Loss	4.52 (382)	-0.42 (382)	-0.70 (205)	-0.71 (217)
≥ 5% Weight Loss	-15.30 (92)	-6.23 (92)	-6.19 (27)	0.94 (30)
All Sibutramine	-8.75 (1164)	-2.21 (1165)	-1.85 (642)	4.13 (664)
< 5% Weight Loss	-0.54 (547)	0.17 (548)	-0.37 (320)	3.19 (331)
≥ 5% Weight Loss	-16.59 (612)	-4.87 (612)	-4.56 (317)	4.68 (328)

Baseline mean values:

Placebo: TG 187 mg/dL; CHOL 221 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

Sibutramine: TG 172 mg/dL; CHOL 215 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL

TG: Triglycerides, CHOL: Cholesterol, LDL-C Low Density Lipoprotein-Cholesterol

HDL-C: High Density Lipoprotein-Cholesterol

Sibutramine induced weight loss has been accompanied by reductions in serum uric acid. Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with cardiac valve dysfunction. The possible occurrence of cardiac valve disease was specifically investigated in two studies. In one study 2-D and color Doppler echocardiography were performed on 210 patients (mean age, 54 years) receiving sibutramine 15 mg or placebo daily for periods of 2 weeks to 16 months (mean duration of treatment, 7.6 months). In patients without a prior history of valvular heart disease, the incidence of valvular heart disease was 3/132 (2.3%) in the sibutramine treatment group (all three cases were mild aortic insufficiency) and 2/77 (2.6%) in the placebo treatment group (one case of mild aortic insufficiency and one case of severe aortic insufficiency). In another study, 25 patients underwent 2-D and color Doppler echocardiography before treatment with sibutramine and again after treatment with sibutramine 5 to 30 mg daily for three months; there were no cases of valvular heart disease.

The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in a 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/m^2 and an average age of 39 years underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean changes from baseline to Week 12 in various measures of ABPM are shown in the following table.

Parameter mm Hg	**Systolic**			**Diastolic**		
	Placebo	**Sibutramine**		**Placebo**	**Sibutramine**	
	n=12	**15 mg n=14**	**20 mg n=16**		**15 mg n=12**	**20 mg n=16**
Daytime	0.2	3.9	4.4	0.5	5.0	5.7
Nighttime	-0.3	4.1	6.4	-1.0	4.3	5.4
Early am	-0.9	9.4	5.3	-3.0	6.7	5.8
24-hour mean	-0.1	4.0	4.7	0.1	5.0	5.6

Normal diurnal variation of blood pressure was maintained.

INDICATIONS AND USAGE

MERIDIA® (sibutramine hydrochloride monohydrate) is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet. MERIDIA is recommended for obese patients with an initial body mass index ≥ 30 kg/m^2, or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).

Below is a chart of Body Mass Index (BMI) based on various heights and weights.

BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in meters, squared. Metric conversions are as follows: pounds ÷ 2.2 = kg; inches x 0.0254 = meters.

BMI		25	26	27	28	29	30	31	32	33	34	35	40
		WEIGHT (lbs)											
	4'10"	119	124	129	134	138	143	149	153	158	163	167	191
	4'11"	124	128	133	138	143	148	154	158	164	169	173	198
	5'	128	133	138	143	148	153	159	164	169	175	179	204
	5'1"	132	137	143	148	153	158	165	169	175	180	185	211
	5'2"	136	142	147	153	158	164	170	175	181	186	191	218
H	5'3"	141	146	152	158	163	169	175	181	187	192	197	225
	5'4"	145	151	157	163	169	174	181	187	193	199	204	232
E	5'5"	150	156	162	168	174	180	187	193	199	205	210	240
	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
I	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
G	5'9"	169	176	182	189	196	203	210	217	224	231	236	270
	5'10"	174	181	188	195	202	207	216	223	230	237	243	278
H	5'11"	179	186	193	200	208	215	222	230	237	244	250	286
	6'	184	191	199	206	213	221	228	236	244	251	258	294
T	6'1"	189	197	204	212	219	227	236	243	251	258	265	302
	6'2"	194	202	210	218	225	233	241	250	258	265	272	311
	6'3"	200	208	216	224	232	240	248	256	264	272	279	319

CONTRAINDICATIONS

MERIDIA is contraindicated in patients:

- with a history of coronary artery disease (e.g., angina, history of myocardial infarction), congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmia or cerebrovascular disease (stroke or transient ischemic attack (TIA)) (see **WARNINGS**).
- with inadequately controlled hypertension > 145/90 mm Hg (see **WARNINGS**).
- over 65 years of age.
- receiving monoamine oxidase inhibitors (MAOIs) (see **WARNINGS**).
- with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.
- who have a major eating disorder (anorexia nervosa or bulimia nervosa).
- taking other centrally acting weight loss drugs.

WARNINGS

Concomitant Cardiovascular Disease

Due to an increased risk of heart attack and stroke in patients with cardiovascular disease, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Blood Pressure and Pulse

MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE AND/OR PULSE RATE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE AND PULSE RATE IS REQUIRED WHEN PRESCRIBING MERIDIA.

In placebo-controlled obesity studies, sibutramine 5 to 20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1 to 3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4 to 5 beats per minute. Larger increases were seen in some patients, particularly when therapy with sibutramine was initiated at the higher doses (see table below). In premarketing placebo-controlled obesity studies, 0.4% of patients treated with sibutramine were discontinued for hypertension (SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with sibutramine were discontinued for tachycardia (pulse rate ≥ 100 bpm), compared with 0.1% in the placebo group. **Blood pressure and pulse should be measured prior to starting therapy with MERIDIA and should be monitored at regular intervals thereafter.** For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension (see **DOSAGE AND ADMINISTRATION**), and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

	% Outliers*		
Dose (mg)	SBP	DBP	Pulse
Placebo	9	7	12
5	6	20	16
10	12	15	28
15	13	17	24
20	14	22	37

*Outlier defined as increase from baseline of ≥15 mm Hg for three consecutive visits (SBP), ≥10 mm Hg for three consecutive visits (DBP), or pulse ≥10 bpm for three consecutive visits.

Potential Interaction With Monoamine Oxidase Inhibitors

MERIDIA is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see **PRECAUTIONS**, Drug Interactions subsection). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA. Similarly, there should be at least a 2-week interval after stopping MERIDIA before starting treatment with MAOIs.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions

The development of a potentially life-threatening serotonin syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions, has been reported with SNRIs and SSRIs alone, including MERIDIA treatment, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms [e.g., nausea, vomiting, diarrhea] (see **PRECAUTIONS, Drug Interactions**). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

Glaucoma

Because MERIDIA can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

Miscellaneous

Organic causes of obesity (e.g., untreated hypothyroidism) should be excluded before prescribing MERIDIA.

PRECAUTIONS

Pulmonary Hypertension

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In premarketing clinical studies, no cases of PPH have been reported with sibutramine capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not MERIDIA may cause this disease.

Seizures

During premarketing testing, seizures were reported in <0.1% of sibutramine treated patients. MERIDIA should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Bleeding

There have been reports of bleeding in patients taking sibutramine. While a causal relationship is unclear, caution is advised in patients predisposed to bleeding events and those taking concomitant medications known to affect hemostasis or platelet function.

Gallstones

Weight loss can precipitate or exacerbate gallstone formation.

Renal Impairment

MERIDIA should be used with caution in patients with mild to moderate renal impairment. MERIDIA should not be used in patients with severe renal impairment, including those with end stage renal disease on dialysis (see **Pharmacokinetics-*Special Populations***-Renal Insufficiency).

Hepatic Dysfunction
Patients with severe hepatic dysfunction have not been systematically studied; MERIDIA should therefore not be used in such patients.

Interference With Cognitive and Motor Performance
Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

Information For Patients
Physicians should instruct their patients to read the Medication Guide before starting therapy with MERIDIA and to reread it each time the prescription is renewed.

Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.

Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan (Imitrex®), or tryptophan, since there is a potential for interactions.

Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

Drug Interactions
CNS Active Drugs: The use of MERIDIA® (sibutramine hydrochloride monohydrate) in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of MERIDIA with other centrally-acting drugs is indicated (see **CONTRAINDICATIONS** and **WARNINGS**).

In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, selegiline) in combination with serotonergic agents (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because sibutramine inhibits serotonin reuptake, MERIDIA should not be used concomitantly with a MAOI (see **CONTRAINDICATIONS**). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA. Similarly, at least 2 weeks should elapse between discontinuation of MERIDIA and initiation of treatment with a MAOI.

The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Because sibutramine inhibits serotonin reuptake, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.

Drugs That May Raise Blood Pressure and/or Heart Rate: Concomitant use of MERIDIA and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.

Alcohol: In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.

Oral Contraceptives: The suppression of ovulation by oral contraceptives was not inhibited by sibutramine. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity
Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.4 and 16 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.

Mutagenicity
Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.

Impairment of Fertility
In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 32 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

Pregnancy
Teratogenic Effects-*Pregnancy Category C*
Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.

No adequate and well controlled studies with sibutramine have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA® (sibutramine hydrochloride monohydrate). Patients should be advised to notify their physician if they become pregnant or intend to become pregnant while taking MERIDIA.

Nursing Mothers
It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatric Use
The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during

the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 130 patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients.

Geriatric Use

Clinical studies of sibutramine did not include sufficient numbers of patients over 65 years of age. Sibutramine is contraindicated in this group of patients (see **CONTRAINDICATIONS**). Pharmacokinetics in elderly patients are discussed in **"CLINICAL PHARMACOLOGY."**

ADVERSE REACTIONS

In placebo-controlled studies, 9% of patients treated with sibutramine (n = 2068) and 7% of patients treated with placebo (n = 884) withdrew for adverse events.

In placebo-controlled studies, the most common events were dry mouth, anorexia, insomnia, constipation and headache. Adverse events in these studies occurring in ≥1% of sibutramine treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
	Sibutramine (n = 2068)	Placebo (n = 884)
BODY SYSTEM Adverse Event	**% Incidence**	**% Incidence**
BODY AS A WHOLE:		
Headache	30.3	18.6
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthenia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.6
RESPIRATORY SYSTEM		
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough increase	3.8	3.3
Laryngitis	1.3	0.9
SKIN & APPENDAGES		
Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8
SPECIAL SENSES		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
UROGENITAL SYSTEM		
Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal monilia	1.2	0.5
Metrorrhagia	1.0	0.8

The following additional adverse events were reported in ≥ 1% of all patients who received sibutramine in controlled and uncontrolled premarketing studies.

Body as a Whole: fever.
Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.
Metabolic and Nutritional: peripheral edema.
Musculoskeletal System: arthritis.
Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.
Respiratory System: bronchitis, dyspnea.
Skin and Appendages: pruritus.
Special Senses: amblyopia.
Urogenital System: menstrual disorders.

Other Adverse Events
Clinical Studies

Seizures: Convulsions were reported as an adverse event in three of 2068 (0.1%) sibutramine treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the three patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; one had a subsequent diagnosis of brain tumor). The incidence in all subjects who received sibutramine (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of sibutramine treated patients and in 0.2% of placebo-treated patients in premarketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. Sibutramine may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in one obese patient receiving sibutramine during premarketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphatase and bilirubin, were reported as adverse events in 1.6% of sibutramine-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥ 2 mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥ 3x upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the sibutramine treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

Postmarketing Reports

Voluntary reports of adverse events temporally associated with the use of sibutramine are listed below. It is important to emphasize that although these events occurred during treatment with sibutramine, they may have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events.

Psychiatric: Cases of depression, psychosis, mania, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between these events and the use of sibutramine. If any of these events should occur during treatment with sibutramine, discontinuation should be considered.

Hypersensitivity: Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported (see **CONTRAINDICATIONS** and **PRECAUTIONS-Information For Patients**, and other reports of allergic reactions listed below).

Other Postmarketing Reported Events:

Body as a Whole: anaphylactic shock, anaphylactoid reaction, chest pressure, chest tightness, facial edema, limb pain, sudden unexplained death.

Cardiovascular System: angina pectoris, atrial fibrillation, congestive heart failure, heart arrest, heart rate decreased, myocardial infarction, supraventricular tachycardia, syncope, torsade de pointes, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation.

Digestive System: cholecystitis, cholelithiasis, duodenal ulcer, eructation, gastrointestinal hemorrhage, increased salivation, intestinal obstruction, mouth ulcer, stomach ulcer, tongue edema.

Endocrine System: goiter, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic System: anemia, leukopenia, lymphadenopathy, petechiae, thrombocytopenia.

Metabolic and Nutritional: hyperglycemia, hypoglycemia.

Musculoskeletal System: arthrosis, bursitis.

Nervous System: abnormal dreams, abnormal gait, amnesia, anger, cerebrovascular accident, concentration impaired, confusion, depression aggravated, Gilles de la Tourette's syndrome, hypesthesia, libido decreased, libido increased, mood changes, nightmares, short term memory loss, speech disorder, transient ischemic attack, tremor, twitch, vertigo.

Respiratory System: epistaxis, nasal congestion, respiratory disorder, yawn.

Skin and Appendages: alopecia, dermatitis, photosensitivity (skin), urticaria.

Special Senses: abnormal vision, blurred vision, dry eye, eye pain, increased intraocular pressure, otitis externa, otitis media, photosensitivity (eyes), tinnitus.

Urogenital System: abnormal ejaculation, hematuria, impotence, increased urinary frequency, micturition difficulty, urinary retention.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MERIDIA is controlled in Schedule IV of the Controlled Substances Act (CSA).

Abuse and Physical and Psychological Dependence

Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE

Overdose Management

There is limited experience of overdose with sibutramine. The most frequently noted adverse events associated with overdose are tachycardia, hypertension, headache and dizziness. Treatment should consist of general measures employed in the management of overdosage: an airway should be established as needed; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. The results from a study in patients with end-stage renal disease on dialysis showed that sibutramine metabolites were not eliminated to a significant degree with hemodialysis. (see **Pharmacokinetics-*Special Populations***-Renal Insufficiency).

DOSAGE AND ADMINISTRATION

The recommended starting dose of MERIDIA is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after four weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration (see **WARNINGS** and **PRECAUTIONS**).

Doses above 15 mg daily are not recommended. In most of the clinical trials, MERIDIA was given in the morning.

Analysis of numerous variables has indicated that approximately 60% of patients who lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA in combination with a reduced-calorie diet lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose of MERIDIA. Conversely, approximately 80% of patients who do not lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA do not lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose. If a patient has not lost at least 4 pounds in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include increasing the dose or discontinuation of MERIDIA.

The safety and effectiveness of MERIDIA, as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 2 years at this time.

HOW SUPPLIED

MERIDIA® (sibutramine hydrochloride monohydrate) Capsules contain 5 mg, 10 mg, or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

5 mg, NDC 0074-2456-12, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 30 capsules.

10 mg, NDC 0074-2457-12, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 30 capsules.

15 mg, NDC 0074-2458-12, yellow/white capsules imprinted with "MERIDIA" on the cap and "-15-" on the body, in bottles of 30 capsules.

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Protect capsules from heat and moisture. Dispense in a tight, light-resistant container as defined in USP.

Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A.
by KNOLL LLC B.V., Jayuya, PR 00664

IMITREX is a registered trademark of Glaxo Group Limited.

MEDICATION GUIDE

MERIDIA® (mer-ID-dee-uh) Ⓒ

(sibutramine hydrochloride monohydrate) Capsules

Read this Medication Guide before you start taking MERIDIA and each time you get a refill. There may be new information. This information does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about MERIDIA?

MERIDIA can cause serious side effects including a large increase in your blood pressure or heart rate (pulse). Do not take MERIDIA if your blood pressure is not well controlled. Call your doctor right away if you check your blood pressure and it is higher than normal for you, or if you have symptoms of high blood pressure such as headache, dizziness or blurred vision.

Before you start taking MERIDIA, your doctor should check your blood pressure and heart rate. Your doctor should continue checking your blood pressure regularly while you are taking MERIDIA. It is important that you have regular check-ups while you are taking MERIDIA.

What is MERIDIA?

MERIDIA is a prescription medicine used to help overweight or obese people lose weight and keep the weight off. MERIDIA should be used together with a low calorie diet.

MERIDIA contains **sibutramine**, a substance that people can become addicted to. Keep your MERIDIA in a safe place to protect it from theft. Never give your MERIDIA to anyone else, because it may cause death or harm them. Selling or giving away this medicine is against the law.

The use of MERIDIA for more than 2 years has not been studied.

It is not known if MERIDIA is safe and effective in children younger than 16 years old.

Who should not take MERIDIA?

Do not take MERIDIA if you:

- have or have had, heart problems, including:
  - heart attack
  - chest pain
  - heart failure
  - fast or irregular heart beat
  - hardening of your arteries or other blood vessels
  - poor circulation in your legs
- have or have ever had, a stroke or symptoms of a stroke
- uncontrolled high blood pressure (above 145/90)
- are over age 65
- are taking or have taken a type of medicine used to treat depression called a monoamine oxidase inhibitor (MAOI) in the past 2 weeks. Do not take MAOIs for at least 2 weeks before using MERIDIA. Do not take MAOIs for at least 2 weeks after stopping MERIDIA. Ask your doctor or pharmacist if you are not sure if any of your medicines are MAOIs.
- have an eating problem called anorexia nervosa or bulimia nervosa.
- are taking certain other weight loss medicines.
- are allergic to sibutramine hydrochloride monohydrate or any other ingredients in MERIDIA. See the end of this Medication Guide for a complete list of ingredients in MERIDIA.

Talk to your doctor before taking this medicine if you have any of these conditions.

What should I tell my doctor before taking MERIDIA?

Before you take MERIDIA, tell your doctor if you:

- have liver or kidney problems
- have glaucoma
- have or had seizures (convulsions, fits)
- have bleeding problems
- have or had gallstones
- are pregnant or plan to become pregnant. It is not known if MERIDIA will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant. If you can become pregnant, you should use birth control while taking MERIDIA. Tell your doctor right away if you become pregnant while taking MERIDIA.
- are breastfeeding or plan to breastfeed. It is not known if MERIDIA passes into your breast milk. You and your doctor should decide if you will take MERIDIA or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using MERIDIA with certain other medicines may affect how MERIDIA or the other medicines work. Using MERIDIA with other medicines can cause serious side effects.

Especially tell your doctor if you take:

- a **monoamine oxidase inhibitors** (MAOIs) medicine. See "**Who should not take MERIDIA?**"
- other weight loss medicines
- cough and cold medicines
- migraine headache medicines like sumatriptan (Imitrex, Imitrex Statdose) or dihydroergotamine (D.H.E 45, Migranal)
- medicines to treat depression
- narcotic pain medicines
- lithium (Lithobid)
- tryptophan
- medicines that thin the blood

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get new medicine.

How should I take MERIDIA?

- Take MERIDIA exactly as your doctor tells you to.
- Take MERIDIA 1 time a day.

- If you miss a dose of MERIDIA, just skip it. Do not take an extra dose to make up for missed doses.
- If you take too much MERIDIA, call your doctor or Poison Control Center right away, or go to the emergency room.
- Your doctor may change your dose if needed.
- Take MERIDIA with or without food.
- You should see your doctor regularly for check-ups.

What should I avoid while taking MERIDIA?

- Do not drive, operate heavy machinery or do other dangerous activities until you know how MERIDIA affects you.
- Do not have more than two standard alcoholic drinks per day while you take MERIDIA.

What are the possible side effects of MERIDIA?

MERIDIA may cause serious side effects, including:

- **See "What is the most important information I should know about MERIDIA?"**
- serotonin syndrome. Serotonin syndrome may happen when people take MERIDIA with certain other medicines that affect a brain chemical called serotonin. Do not take other medicines with MERIDIA unless your doctor has told you to. Get medical help right away if you have any of the following symptoms:
  - feel weak, restless, confused, or anxious
  - lose consciousness (faint)
  - have a fever, vomiting, sweating, shivering or shaking
  - have a fast heartbeat
- seizures (convulsions, fits)
- bleeding. Bleeding may happen if you have a condition that causes bleeding or if you take a blood thinning medicine.

Certain weight loss medicines have a rare but life-threatening problem that affects blood pressure in the lungs (pulmonary hypertension). It is not known if MERIDIA may cause this problem because pulmonary hypertension is so rare. Call your doctor right away if you have new or worsening shortness of breath.

The most common side effects of MERIDIA include:

- dry mouth
- loss of appetite
- trouble sleeping
- constipation
- headache

Tell your doctor if you get a rash or hives while taking MERIDIA. You may be having an allergic reaction.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the side effects of MERIDIA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MERIDIA?

- Store MERIDIA between 59°F to 86° F (15°C to 30° C).
- Keep MERIDIA capsules dry and away from heat.
- Keep MERIDIA in a tightly closed container, and keep MERIDIA out of the light.
- Safely throw away medicine that is out of date or no longer needed.

Keep MERIDIA and all medicines out of reach of children.

General information about MERIDIA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MERIDIA for a condition for which it was not prescribed. Do not give MERIDIA to other people, even if they have the same symptoms you have. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about MERIDIA. If you would like more information, talk with your doctor. You can also ask your doctor or pharmacist for information about MERIDIA that is written for health professionals.

For more information, go to www.Meridia.net, or call 1-800-633-9110.

What are the ingredients in MERIDIA?

Active ingredient: sibutramine hydrochloride monohydrate

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate.

Hard-gelatin capsule: titanium dioxide, gelatin, FD&C Blue No. 2 (5 mg and 10 mg capsules only), D&C Yellow No. 10 (5 mg and 15 mg capsules only), and other inactive ingredients.

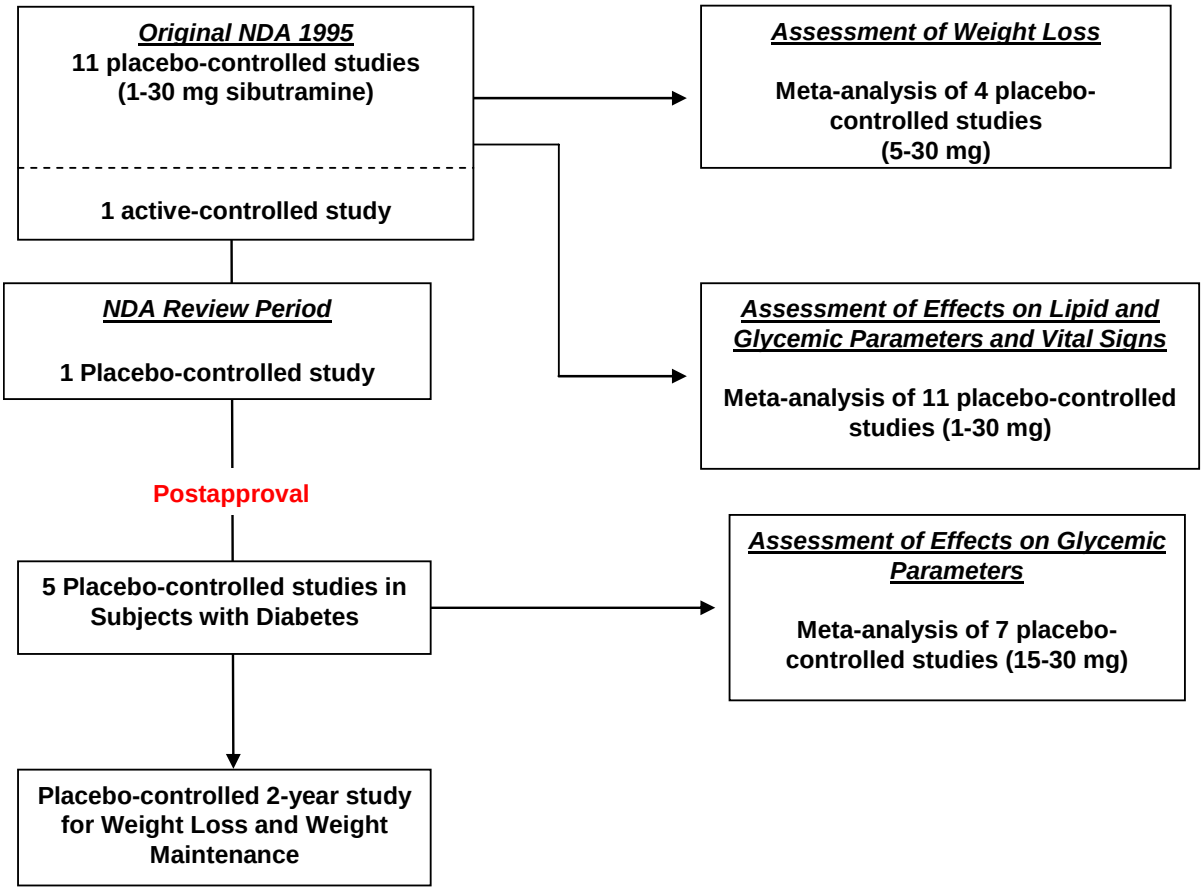
Manufactured for Abbott Laboratories, North Chicago, IL 60064, U.S.A.
by KNOLL LLC B.V., Jayuya, PR 00664

This Medication Guide has been approved by the U.S. Food and Drug Administration.

DN2155V1 (03-A373)

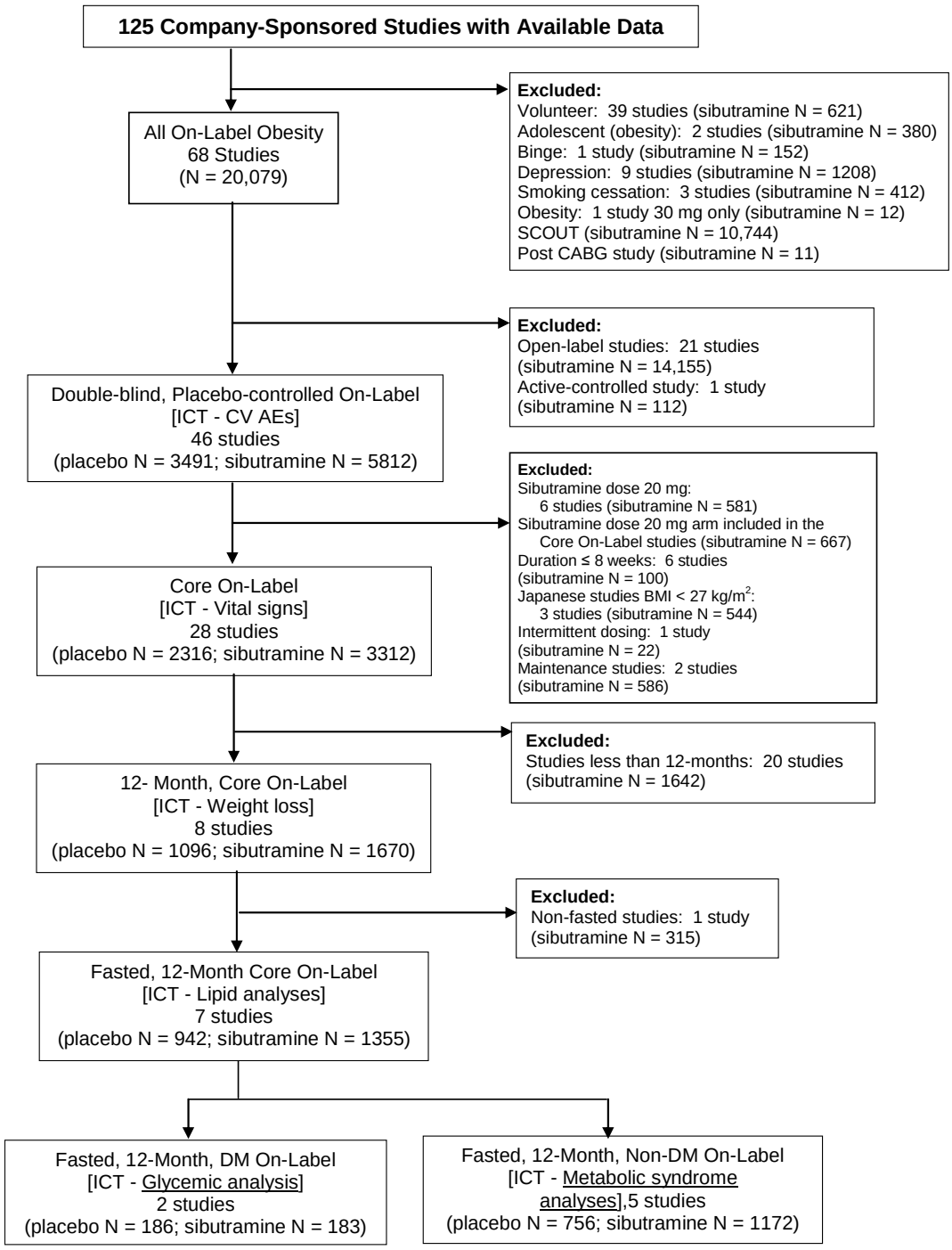
Appendix B. Clinical Studies Assessed in the US Registration Package

Clinical Studies Assessed in the US Registration Package



Appendix C. Algorithm for Study Selection for the Integrated Clinical Trials

Algorithm for Study Selection for the Integrated Clinical Trials



Appendix D. Governance Bodies: Roles and Responsibilities

SCOUT Governance Bodies

The study was overseen by an executive steering committee (ESC) and monitored by an independent data safety monitoring board (DSMB) in accordance with standard conduct for clinical outcome studies. An events adjudication committee (EAC) was utilized to review all potential outcomes events occurring during the study.

Members of these governance bodies and the EAC were precluded from acting as trial investigators or being members of the other governance bodies for the study.

Executive Steering Committee

Membership:

Members of the ESC were a multidisciplinary group who collectively had the scientific, medical, and clinical study management experience to conduct and evaluate the study.

Responsibilities:

The key responsibilities of the ESC were:

- Safeguarded the interests of participating subjects and for the conduct of the study jointly with the DSMB.
- Provided advice to the DSMB on all scientific and clinical aspects related to sibutramine.
- Reviewed recommendations from the DSMB Chairperson and determined whether amendments to the protocol or study conduct were necessary.
- Consulted with the DSMB on substantive changes to the protocol or study conduct and provided Abbott with any recommended changes.

Data Safety Monitoring Board

Membership:

The DSMB was an independent, multidisciplinary group consisting of 5 clinicians and 1 biostatistician who, collectively, had experience in cardiology and in the treatment of subjects with obesity and in the conduct and monitoring of randomized clinical trials.

Responsibilities:

The DSMB was established to provide an independent review and assessment of the safety and efficacy data and to further safeguard the interests and safety of the participating subjects.

The key responsibilities included the following:

- Ensured the ongoing safety of study participants and the scientific integrity of the study and the validity and scientific merit of the study.
- Monitored the conduct of the study.
- Reviewed interim results for the purpose of recommending to the ESC whether or not to continue, modify or terminate the study.

The DSMB used formal criteria to determine whether to recommend stopping SCOUT for either overwhelming benefit or unacceptable harm. These formal criteria were to be used in conjunction with all available information in making recommendations to the ESC.

The ESC was responsible for accepting or rejecting the DSMB recommendations. During the conduct of the study, there were no circumstances where Abbott is aware of the ESC not following the recommendation of the DSMB.

Formal meetings occurred 9 times during the study (approximately every 6 months).

Events Adjudication Committee

Membership:

The EAC Chairman was responsible for the nomination of EAC members and their coordination. The EAC Chairman was also responsible for the quality control of the adjudication process.

Responsibilities:

The primary role of the EAC was to perform the timely review of all potential outcome events that occurred during the study (Lead-in Period and Randomization Phase) and to adjudicate whether they met the criteria of an outcome event as defined in the EAC manual. All events that were judged by the EAC to be outcome events were categorized by the EAC into one or more categories according to the definitions outlined in the EAC manual. EAC members were blinded to assigned study arms (sibutramine or placebo) for potential outcome events that occurred during the randomization phase, but were made aware of the timing of the event (i.e., Lead-in Period, Treatment Period, or Follow-up Period).

The EAC were required to establish the date(s) of each categorized event after the review of the data as completed by the investigative site and other required supportive documentation. The EAC did not liaise directly with study investigators.

The EAC were not responsible for any safety assessment of the study. The responsibility for safety assessment remained with the DSMB, which acted independently from the sponsor, the ESC, and the EAC.

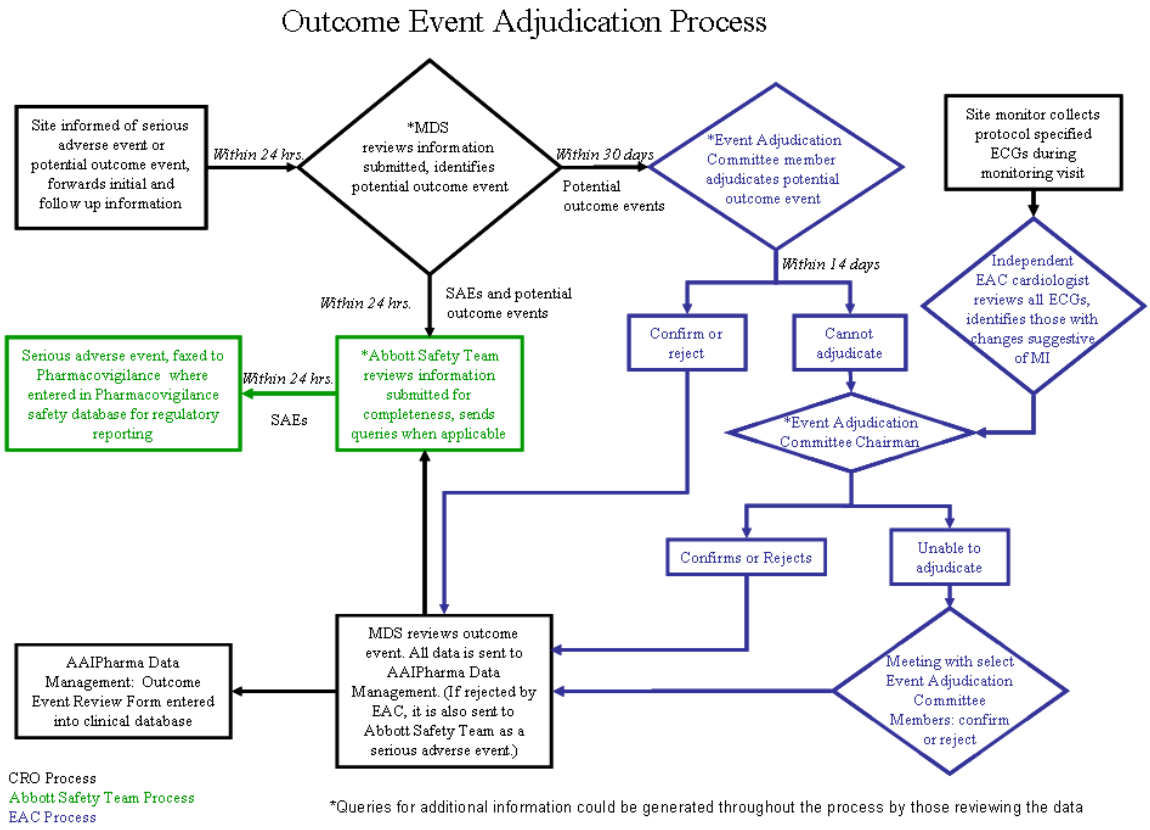
Appendix E. Outcome Events Adjudication Process

Outcome Events Adjudication Process

In the SCOUT trial, nonfatal myocardial infarction (MI), nonfatal stroke, resuscitated cardiac arrest, cardiovascular death, and non-cardiovascular death were considered outcome events (OEs) that were adjudicated and confirmed by an independent Event Adjudication Committee (EAC) which was blinded to subjects' Treatment Period study drug assignment. The adjudication was based on an event adjudication manual with detailed definitions of outcome events and their required documentation. Brief descriptions of the outcome events are provided in the table below. The EAC was composed of 12 individuals with recognized expertise in cardiology and neurology.

Outcome Event	Description
Nonfatal Myocardial Infarction	Nonfatal MI is considered either as a "natural" occurring event (non-periprocedural event) or as related to a diagnostic or therapeutic intervention (periprocedural event). An increase in biomarkers ([troponin I or T] and/or cardiac enzymes) is required for a diagnosis of all non-periprocedural MIs except for unrecognized MI (silent MI). In addition to silent MIs reported by the investigator, protocol scheduled ECGs were reviewed by an independent cardiologist for changes suggestive of an unrecognized silent MI.
Nonfatal Stroke	Stroke is defined as the presence of acute focal neurological deficit thought to be of vascular origin with symptoms and/or signs lasting more than 24 hours. Subarachnoid hemorrhage may not have focal deficit however, would qualify as stroke. The date of the event will be determined by the EAC Member based on clinical symptoms and/or diagnostic tests (CT scan or magnetic resonance imaging [MRI]).
Resuscitated Cardiac Arrest	Resuscitated cardiac arrest is defined as cardiac arrest with or without symptoms or signs of MI, arrhythmia or heart failure with return to cardiac function by cardioversion, defibrillation or cardiopulmonary resuscitation interventions. Patients on life support apparatus do not qualify.
Cardiovascular Death	Cardiovascular death includes sudden death, un-witnessed unexpected death, fatal MI, death from heart failure, death from arrhythmia, fatal stroke, death due to cardiovascular causes related to invasive diagnostic or therapeutic procedures, death due to other cardiovascular causes, death due to presumed cardiovascular causes and death from unknown cause. (Of note: if death occurred within 30 days of either the event of MI or stroke, the event was considered a fatal MI or fatal stroke.)
Non-Cardiovascular Death	Death without well-documented non-cardiovascular etiology will be considered cardiovascular death. Non-cardiovascular death cases will require a well-documented etiology and will be classified as cancer death or non-cancer death.

The adjudication process for these OEs in the SCOUT trial is described in the following flow chart, with additional explanation provided below.



Site personnel reported all serious adverse events (SAEs) and any potential OEs as defined by the protocol, using a common case report form for both types of events. All events were reported to MDS Pharma Services (MDS) without distinction.

Medical Safety Officers (at MDS) reviewed the submitted information for each event to determine if the event could potentially meet the predefined criteria for an OE described in the Event Adjudication Manual for the SCOUT study. In addition, a medical review assessed whether the required supportive documentation for the outcome event was collected. Requests for additional information could be made to the site as deemed necessary for the adjudication process. All potential OEs and respective follow-up

information were forwarded to EAC for adjudication. All information (initial and follow-up) provided to MDS was also forwarded to Abbott for additional review of completeness.

Adjudication was performed by an EAC member utilizing the guidelines and detailed definitions of each possible outcome contained in the Event Adjudication Manual that included specific clinical evidence corroborated by other objective means (e.g., CT scan for stroke).

The EAC member could adjudicate the event in 1 of 3 ways:

- Confirm the event as an OE
- Reject the event as an OE
- Unable to adjudicate the event with information provided

The EAC member could request additional information for adjudication. The EAC member categorized each confirmed OE according to the type of MI, type of stroke, resuscitated cardiac arrest, type of cardiovascular death, or type of non-cardiovascular death and established the date of each OE. If there were multiple events reported for a given patient, the EAC adjudicated each event independently and established the date for each event. For fatal MIs and fatal strokes, both the date of the MI/stroke and the date of death were established.

If an event was rejected as an OE, MDS notified the Abbott Safety Team of the event status change. The Abbott Safety Team reviewed the information received from MDS and, dependent upon seriousness criteria, processed the event as an AE or SAE.

If unable to adjudicate the event, the information was routed to the EAC Chairman for adjudication. If the EAC Chairman was unable to adjudicate the potential OE, it was re-reviewed at a later date by selected EAC members and the EAC Chairman which made a decision to either reject or confirm the OE.

In a separate process, protocol-scheduled ECGs were reviewed by an independent cardiologist within the EAC. ECGs with changes suggesting potential MIs were identified and sent for further adjudication. Upon confirmation by the EAC, ECG changes confirmed as silent MIs were categorized as nonfatal MIs.

The EAC member documented the adjudication decision on Outcome Event Review form(s) and submitted it to MDS Pharma Services, who reviewed the form(s) for completeness and forwarded it to AAI Pharma, a Data Management CRO, to be entered into the clinical database.

Appendix F. Analysis of Investigator-Reported Adverse Events: List of MedDRA SMQs, Preferred Terms, or SOC Used to Identify Potential POE

Analysis of Investigator-Reported Adverse Events: List of MedDRA SMQs, Preferred Terms, or SOC Used to Identify Potential POE

In order to identify the relevant adverse events corresponding to each of the 4 POE components, the following Standardized MedDRA Query (SMQ) search strategy was used:

POE Component	Corresponding MedDRA Preferred Terms, Standardized MedDRA Query (SMQ), or System Organ Class
Nonfatal MI	Myocardial infarction SMQ (narrow scope)
Nonfatal stroke	Ischemic cerebrovascular conditions SMQ (narrow scope)
Resuscitated cardiac arrest*	Preferred terms: Cardiac arrest Cardiac death Cardiac fibrillation Cardio-respiratory arrest Sudden cardiac death Sudden death Ventricular fibrillation External counterpulsation Cardioversion Defibrillation threshold increased Resuscitation
CV death	Any fatal event under the Cardiovascular system organ class

* Nonfatal events

Appendix G. Statistical Appendix

Treatment-by-Subgroup Interaction Tests

POE

The patterns manifested in the Kaplan-Meier curves and in their corresponding cumulative incidence rates are consistent with the proportional hazards assumption for the ITT population and for the non–DM Only group (the combined CV only and CV + DM subgroups), but not for the DM Only group. In the DM Only group, the event rate is lower for sibutramine than for placebo for the first 3+ years of treatment but is approximately equal between treatment groups at Years 4 and 5. The pattern for the non–DM Only group is consistent with a treatment effect gradually emerging over time.

Estimates of cumulative yearly event rates from these Kaplan-Meier curves for each CV risk subgroup, the corresponding treatment differences, and the *P* value for the test for treatment-by–CV risk group interaction are summarized in Table 1a.

Table 1a. Results of Treatment-by-CV Risk Group Interaction Test for the POE (DM Only Group Versus Non-DM Only Group)

Treatment Duration	DM Only Group Event Rates			Non–DM Only Group Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	1.41%	0.79%	–0.62%	2.49%	3.22%	0.73%	0.021*
Year 0 – 2	2.29%	1.75%	–0.54%	5.50%	6.27%	0.77%	0.104
Year 0 – 3	3.88%	2.98%	–0.90%	7.92%	9.60%	1.68%	0.011*
Year 0 – 4	5.14%	4.85%	–0.29%	10.62%	12.21%	1.59%	0.112
Year 0 – 5	6.11%	5.88%	–0.23%	12.79%	14.84%	2.05%	0.094*

* Statistically significant at the 0.10 level.

For the DM Only group, the Kaplan-Meier estimates for the primary endpoint event rate were generally lower for sibutramine than for placebo; by up to 0.90% for the first 3 years of treatment, but by Year 4 these differences had been substantially reduced. For the non–DM Only group, the event rate estimates were higher for sibutramine than for

placebo, by 0.73% for the first year, and this difference generally increased over time, reaching 2.05% by Year 5.

Tests of the treatment-by–CV risk subgroup interaction (DM Only versus the combined CV Only and CV + DM groups) were performed on an absolute scale, using the appropriate linear contrast of the Kaplan-Meier–based estimates of event rates, and its standard error based on the variances of these Kaplan-Meier estimates. These interaction tests were performed to assess whether the treatment differences for the DM Only group were statistically significantly different from those of the other 2 CV risk groups combined. A statistically significant interaction effect (at the 0.10 level) was obtained for Year 1 and Year 3 (P = 0.021, 0.011, and 0.094, respectively). No other statistically significant results were obtained.

These results support the use of separate analyses of POE for the DM Only group, especially for the first 3 years of treatment.

Similar patterns for the Kaplan-Meier curves and their corresponding cumulative incidence rates are apparent for the DM Only Without CV Contraindications subpopulation versus the other groups combined (CV Only, CV + DM, and DM Only with CV contraindications). Results are presented in Table 1b:

Table 1b. Results of Treatment-by-CV Risk Group Interaction Test for the POE (DM Only Without CV Contraindications Versus All Other Groups)

Treatment Duration	DM Only without CV Contraindications Event Rates			All Other Groups Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	1.46%	0.56%	–0.90%	2.41%	3.11%	0.70%	0.008*
Year 0 – 2	2.13%	1.58%	–0.55%	5.34%	6.02%	0.68%	0.138
Year 0 – 3	3.60%	2.38%	–1.22%	7.74%	9.30%	1.56%	0.006*
Year 0 – 4	4.40%	3.98%	–0.42%	10.45%	11.94%	1.49%	0.111
Year 0 – 5	5.35%	4.88%	–0.47%	12.50%	14.48%	1.98%	0.072*

* Statistically significant at the 0.10 level.

For the DM only Without CV Contraindications subpopulation, the Kaplan-Meier estimates for the primary endpoint event rate were generally lower for sibutramine than for placebo by up to 1.22% for the first 3 years of treatment, but by Year 4 and Year 5 these differences had declined to 0.42% and 0.47%. For all other groups, the event rate estimates were higher for sibutramine than for placebo for each year; by 0.70% for the first year, and this difference generally increased over time, reaching 1.98% by Year 5.

Tests of the treatment-by–CV risk subgroup interaction (DM Only Without CV Contraindications versus the combination of all other groups) were performed in the same manner as for those in Table 1a. A statistically significant interaction effect (at the 0.10 level) was obtained for Year 1, Year 3, and Year 5 (P = 0.008, 0.006, and 0.072, respectively). No other statistically significant results were obtained.

These results support the use of separate analyses of the POE for the DM Only Without CV Contraindications subpopulation, especially for the first 3 years of treatment.

Similar patterns for the Kaplan-Meier curves and their corresponding cumulative incidence rates are apparent for the DM Only Indicated per US Label subpopulation versus the other groups combined. Results are presented in Table 1c:

Table 1c. Results of Treatment-by-CV Risk Group Interaction Test for the POE (DM Only Indicated per US Label Versus All Other Groups)

Treatment Duration	DM Only Indicated per US Label Event Rates			All other Groups Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	0.51%	0.00%	–0.51%	2.38%	2.86%	0.48%	0.045*
Year 0 – 2	1.29%	1.07%	–0.22%	5.04%	5.56%	0.52%	0.423
Year 0 – 3	2.07%	2.15%	0.08%	7.39%	8.53%	1.14%	0.373
Year 0 – 4	2.33%	2.96%	0.63%	9.90%	11.07%	1.17%	0.684
Year 0 – 5	3.16%	4.22%	1.06%	11.73%	13.22%	1.49%	0.782

* Statistically significant at the 0.10 level.

For the DM Only Indicated per US Label subpopulation, the Kaplan-Meier estimates for the primary endpoint event rate were lower for sibutramine than for placebo by 0.51% to 0.22% by the first 1 and first 2 years of treatment, respectively, but by Year 3 these differences had reversed. For all other groups, the event rate estimates were higher for sibutramine than for placebo, by 0.48% for the first year, and this difference increased over time, reaching 1.49% by Year 5. For each treatment duration, the difference between sibutramine and placebo was smaller for the DM Only Indicated per US Label subpopulation than for the other groups.

Tests of the treatment-by–subgroup interaction were performed in the same manner as for Table 1a. A statistically significant interaction effect (at the 0.10 level) was obtained for Year 1 ($P = 0.045$). The interaction was not statistically significant for any other treatment durations.

These results support the use of separate analyses of the DM Only Indicated per US Label subpopulation, especially for the first year of treatment.

All-Cause Mortality

The patterns manifested in the in the Kaplan-Meier curves and in their corresponding cumulative All-Cause Mortality rates and in the Kaplan-Meier curves are consistent with

the proportional hazards assumption for the ITT population and for the non–DM Only group, but not for the DM Only group. In the DM Only group, the event rate is lower for sibutramine than for placebo well beyond the first 3 years of treatment, and is approximately equal between treatment groups beginning at Year 4.

Estimates of cumulative yearly event rates from these Kaplan-Meier curves for the 2 CV risk groups, the corresponding treatment differences, and the *P* value for the test for treatment-by–CV risk group interaction are summarized in Table 2a.

Table 2a. Results of Treatment-by-CV Risk Group Interaction Test for All-Cause Mortality (DM Only Group Versus Non-DM Only Group)

Treatment Duration	DM Only Group Event Rates			Non–DM Only Group Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	0.88%	0.26%	–0.62%	1.23%	1.45%	0.22%	0.044*
Year 0 – 2	1.58%	0.52%	–1.06%	3.24%	3.11%	–0.13%	0.116
Year 0 – 3	3.25%	1.75%	–1.50%	5.36%	5.93%	0.57%	0.014*
Year 0 – 4	3.87%	3.43%	–0.44%	8.36%	8.53%	0.17%	0.552
Year 0 – 5	5.11%	5.21%	0.10%	10.54%	11.16%	0.62%	0.678

* Statistically significant at the 0.10 level.

For the DM Only group, the Kaplan-Meier estimates for All-Cause Mortality were lower for sibutramine than for placebo by up to 1.50% for the first 3 years of treatment, but by Year 4 this advantage had been reduced to 0.44%, and the sibutramine rate was higher than that of placebo by 0.10% by Year 5. For the other 2 CV risk groups, the event rate estimates were generally higher for sibutramine than for placebo, reaching 0.62% by Year 5.

Tests of the treatment-by–CV risk subgroup interaction (DM Only versus the combined CV Only and CV + DM groups) were performed on an absolute scale, using the appropriate linear contrast of the Kaplan-Meier–based estimates of event rates, and its standard error based on the variances of these Kaplan-Meier estimates. These interaction

tests were performed to determine whether the treatment differences for the DM Only group were statistically significantly different from those of the non–DM Only group. A statistically significant interaction effect (at the 0.10 level) was obtained for Year 1 and Year 3 (P = 0.044 and 0.014, respectively). No other statistically significant results were obtained.

These results support the use of separate analyses of All-Cause Mortality for the DM Only group, especially for the first 3 years of treatment.

Similar patterns for the Kaplan-Meier curves and their corresponding cumulative All-Cause Mortality rates are apparent for the DM Only Without CV Contraindications subpopulation versus the other groups combined (CV Only, CV + DM, and DM Only with CV contraindications). Results are presented in Table 2b:

Table 2b. Results of Treatment-by-CV Risk Group Interaction Test for All-Cause Mortality (DM Only Without CV Contraindications Versus All Other Groups)

Treatment Duration	DM Only without CV Contraindications Event Rates			All other Groups Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	0.89%	0.23%	–0.66%	1.20%	1.38%	0.18%	0.052*
Year 0 – 2	1.57%	0.45%	–1.12%	3.14%	2.96%	–0.18%	0.126
Year 0 – 3	3.13%	1.36%	–1.77%	5.26%	5.75%	0.49%	0.009*
Year 0 – 4	3.24%	2.83%	–0.41%	8.22%	8.33%	0.11%	0.615
Year 0 – 5	4.06%	4.42%	0.36%	10.53%	11.00%	0.47%	0.934

* Statistically significant at the 0.10 level

For the DM Only Without CV Contraindications subpopulation, the Kaplan-Meier estimates for the primary endpoint event rate were generally lower for sibutramine than for placebo; by up to 1.77% for the first 3 years of treatment, but by Year 4 these differences had diminished and then reversed at Year 5. For all other groups, the event rate estimates were generally higher for sibutramine than for placebo, by up to 0.49%.

Tests of the treatment-by–CV risk subgroup interaction (DM Only Without CV Contraindications versus all other groups combined) were performed in the same manner as for Table 1a. A statistically significant interaction effect (at the 0.10 level) was obtained for Year 1 and Year 3 (P = 0.052 and 0.009, respectively). No other statistically significant results were obtained.

These results support the use of separate analyses of All-Cause Mortality for the DM Only Without CV Contraindications subpopulation, especially for the first 3 years of treatment.

Similar patterns for the Kaplan-Meier curves and their corresponding cumulative all-cause mortality rates are apparent for the DM Only Indicated per US Label subpopulation versus the other groups combined. Results are presented in Table 2c:

Table 2c. Results of Treatment-by-CV Risk Group Interaction Test for All-Cause Mortality (DM Only Indicated per US Label Versus All Other Groups)

Treatment Duration	DM Only Indicated per US Label Event Rates			All Other Groups Event Rates			Interaction *P* value
	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	Placebo	Sibutramine	Difference (Sibutramine–Placebo)	
Year 0 – 1	0.00%	0.27%	0.27%	1.24%	1.24%	0.00%	0.442
Year 0 – 2	1.03%	0.53%	–0.50%	3.00%	2.68%	–0.32%	0.816
Year 0 – 3	1.80%	1.60%	–0.20%	5.12%	5.24%	0.12%	0.769
Year 0 – 4	1.80%	2.68%	0.88%	7.73%	7.68%	–0.05%	0.446
Year 0 – 5	2.58%	3.91%	1.33%	9.72%	10.16%	0.44%	0.554

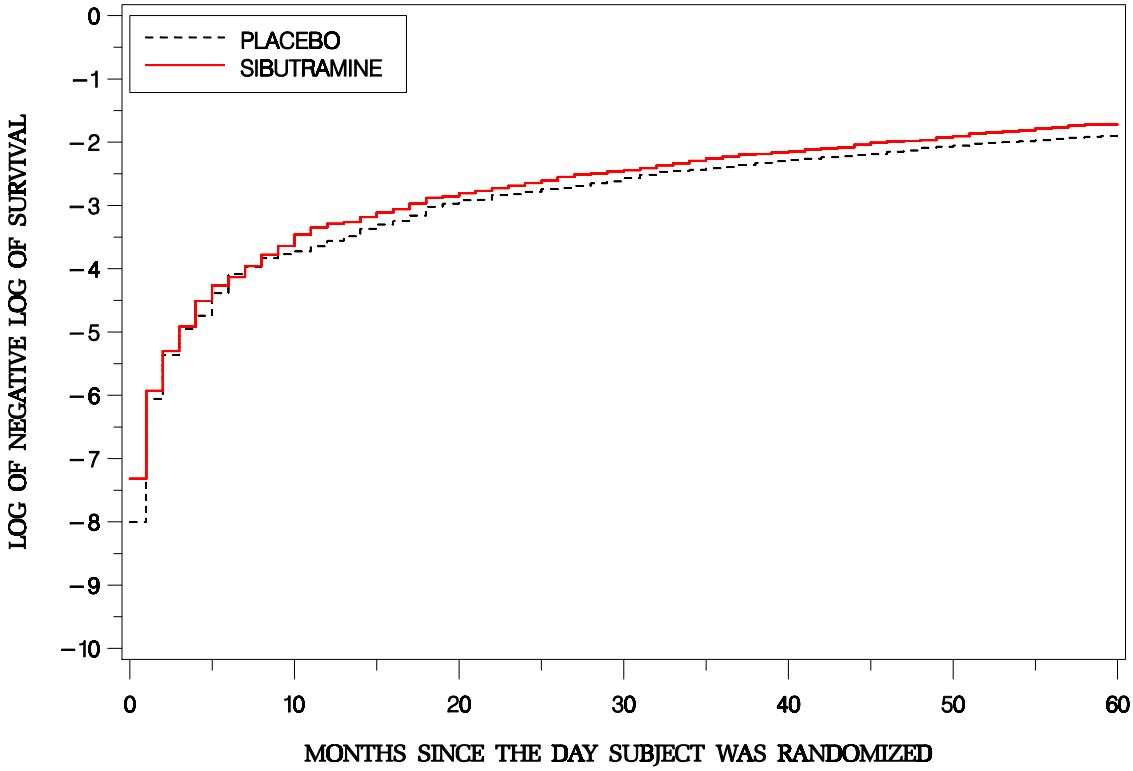
For the DM Only Indicated per US Label subpopulation, the Kaplan-Meier estimates for the primary endpoint event rate were lower for sibutramine than for placebo by the second and third year of treatment; by 0.50% to 0.20%, respectively, but by Year 4 these differences had reversed. For all other groups, the event rate estimates were different between sibutramine and placebo by up to 0.44%. For each treatment duration, the

difference between sibutramine and placebo for the DM Only Indicated per US Label subpopulation differed from that for the other groups by less than 1.0%.

Tests of the treatment-by–subgroup interaction were performed in the same manner as for Table 1a. There were no statistically significant interaction effects. These results are consistent with the fact that results for all-cause mortality for the DM Only Indicated per US Label subpopulation do not appreciably differ from those based on the ITT population.

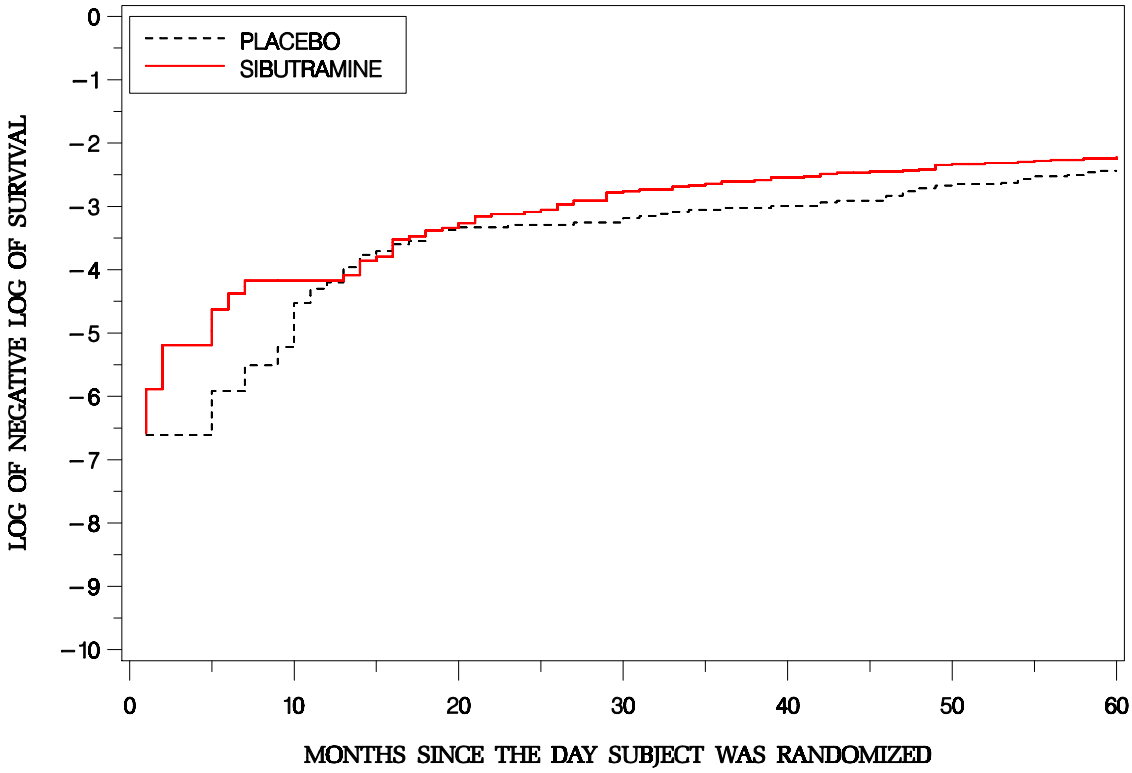
Log-Log Plots

Figure 1. Log-Log Hazard Plot of Primary Outcome Events for the CV + DM Group: ITT Population



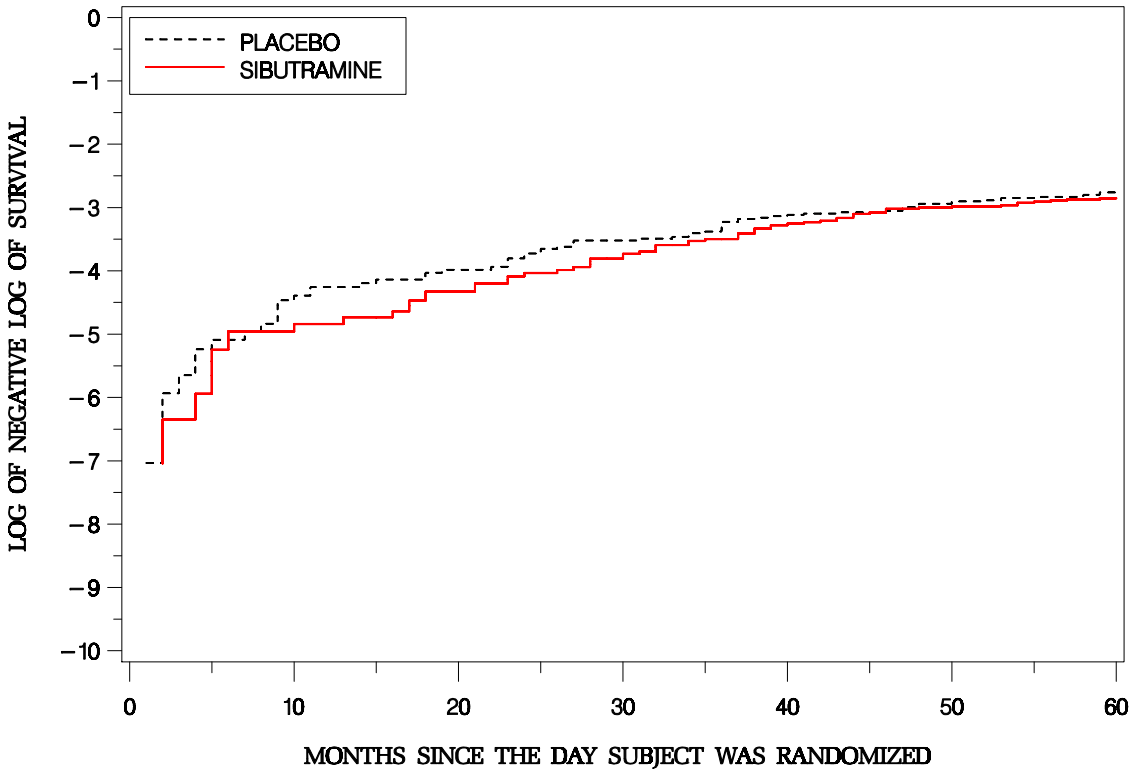
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 2. Log-Log Hazard Plot of Primary Outcome Events for the CV Only Group: ITT Population



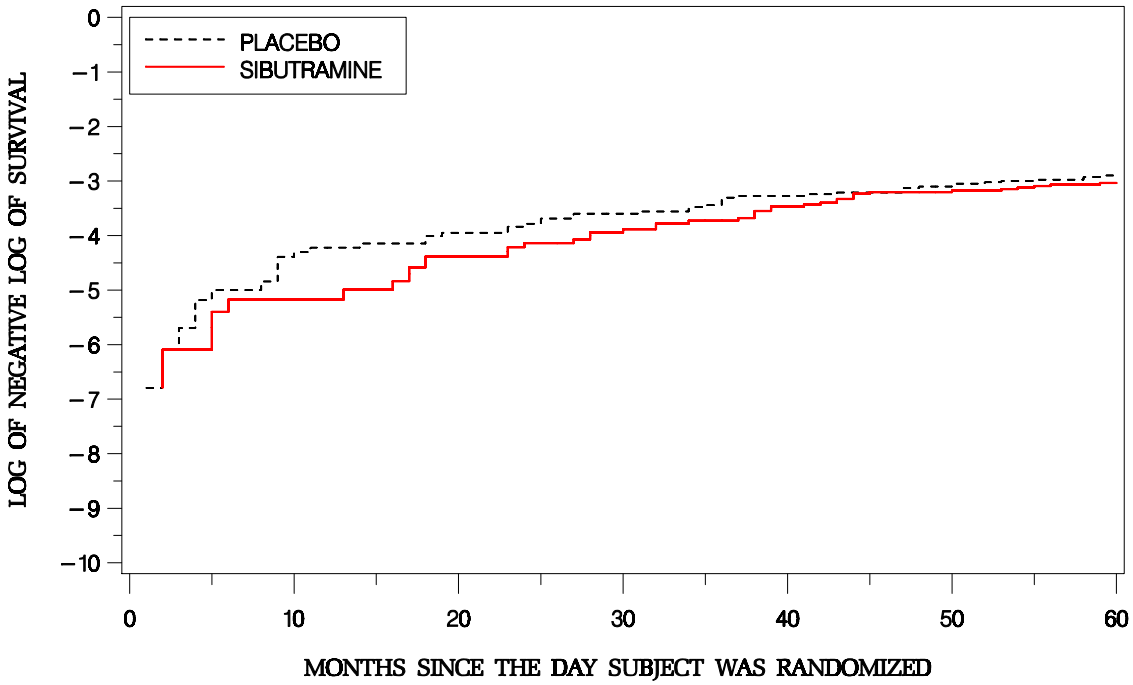
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 3. Log-Log Hazard Plot of Primary Outcome Events for the DM Only Group: ITT Population



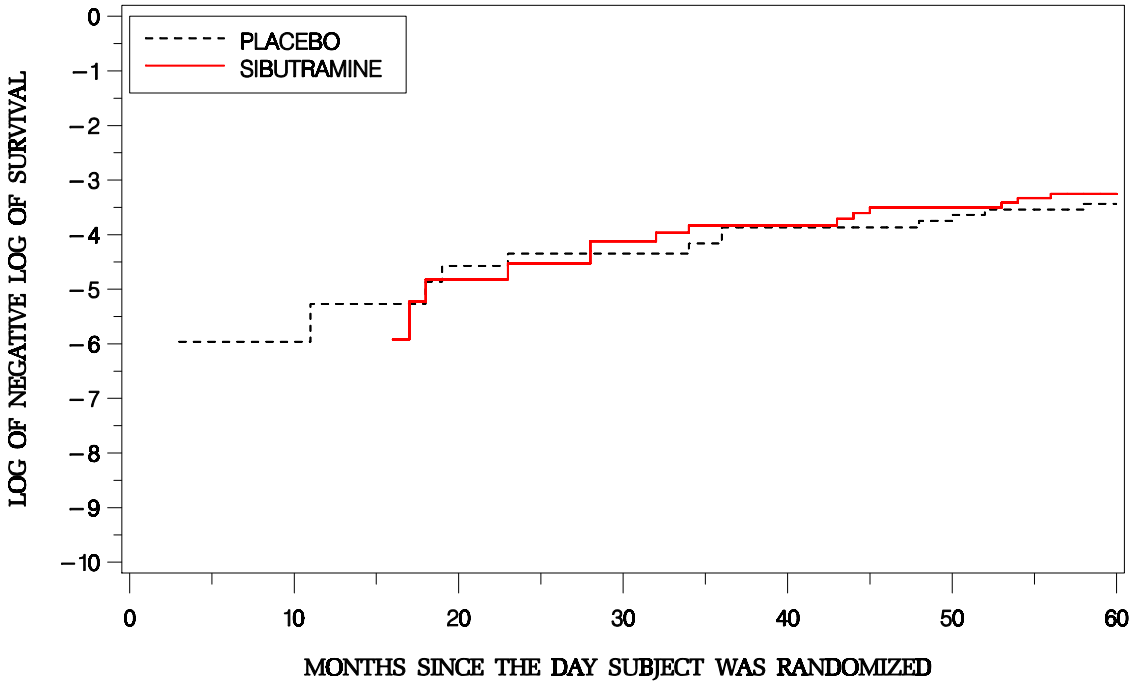
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 4. Log-Log Hazard Plot of Primary Outcome Events for the DM Only Without CV Contraindications Subpopulation: ITT Population



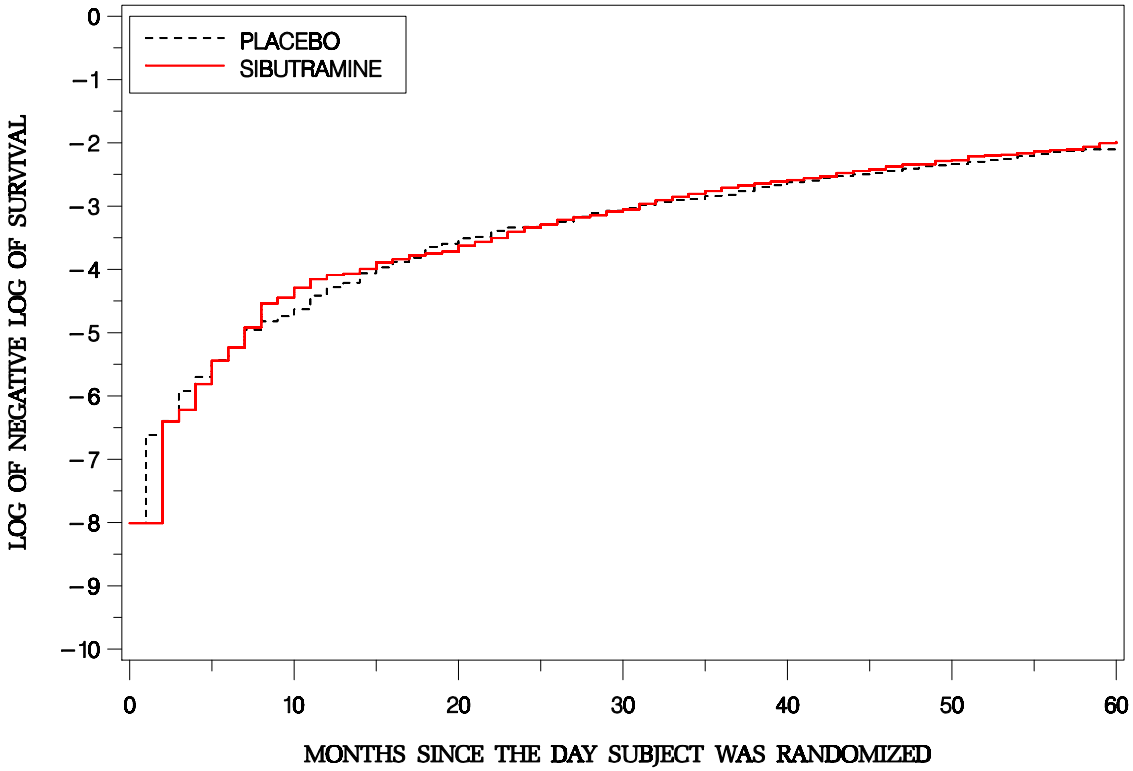
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 5. Log-Log Hazard Plot of Primary Outcome Events for the DM Only Indicated per US Label Subpopulation: ITT Population



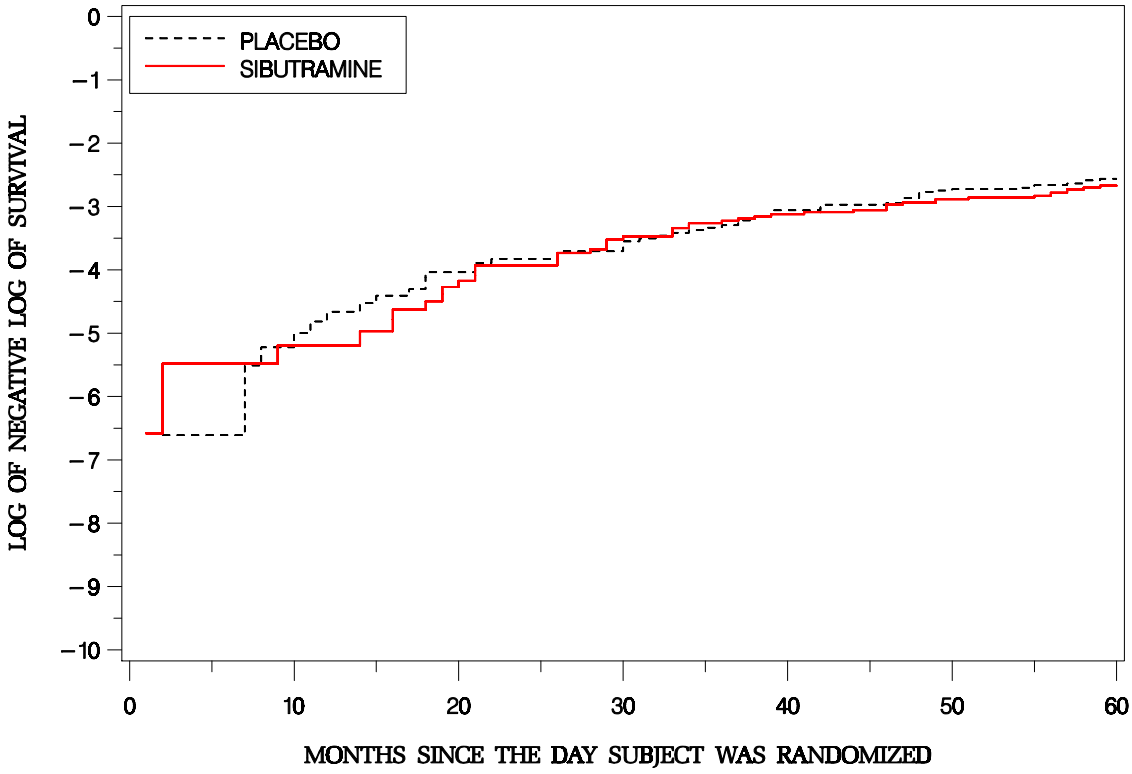
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 6. Log-Log Hazard Plot of Death Due to Any Cause for the CV + DM Group: ITT Population



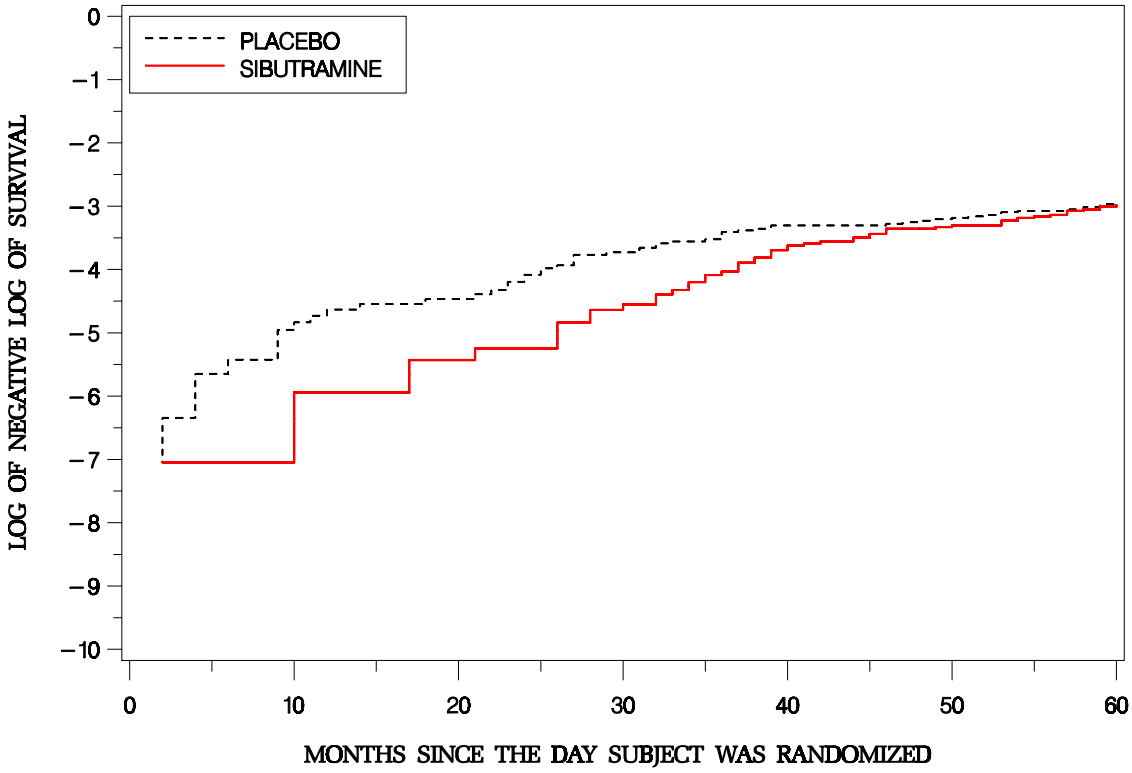
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 7. Log-Log Hazard Plot of Death Due to Any Cause for the CV Only Group: ITT Population



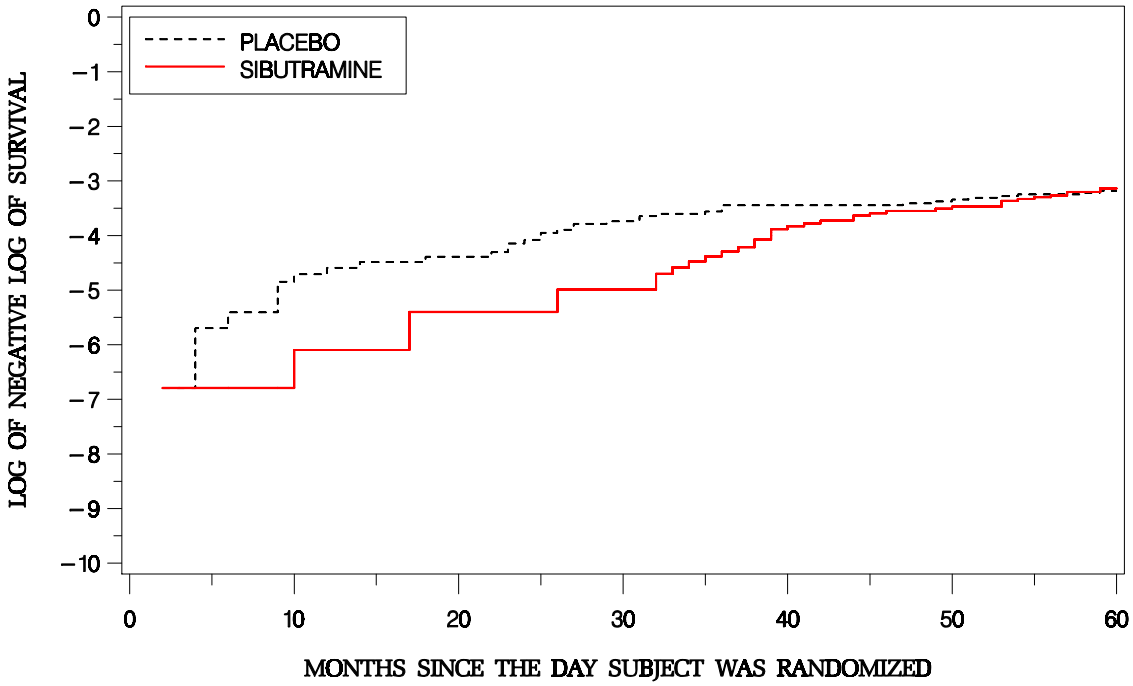
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 8. Log-Log Hazard Plot of Death Due to Any Cause for the DM Only Group: ITT Population



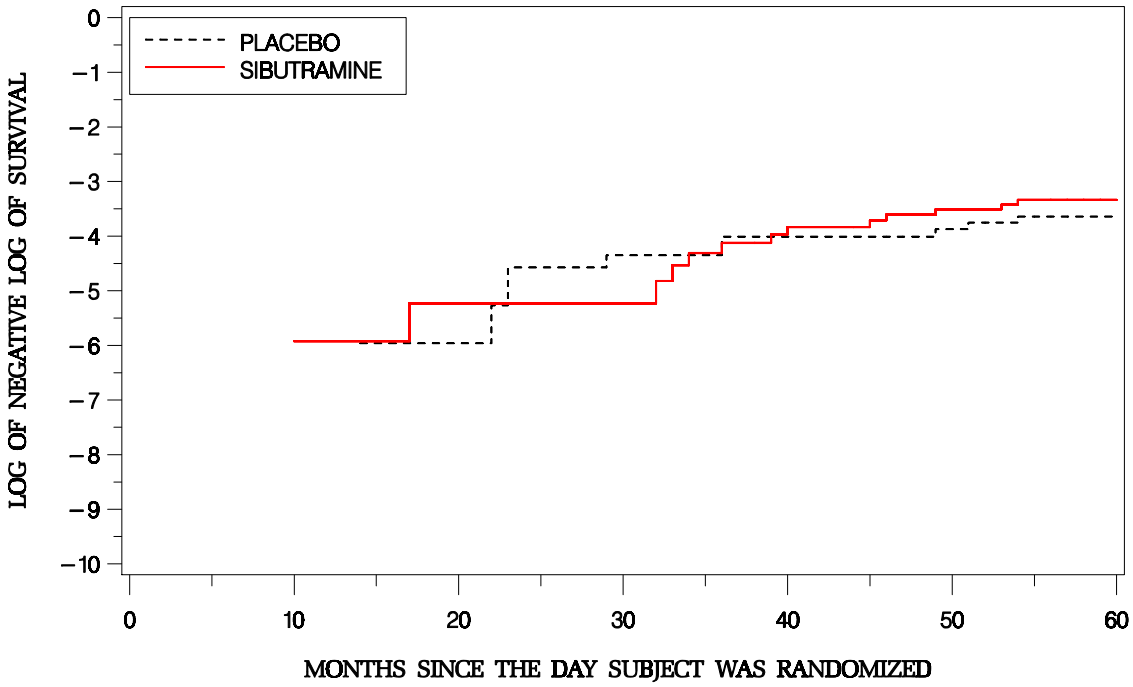
Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 9. Log-Log Hazard Plot of Death Due to Any Cause for the DM Only Without CV Contraindications Subpopulation: ITT Population



Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Figure 10. Log-Log Hazard Plot of Death Due to Any Cause for the DM Only Indicated per US Label Subpopulation: ITT Population



Note: Plot has been truncated at Month 60 for graphical purposes while all data was included in the analysis.

Appendix H. Risk Management Plan

Risk Management Plan

On the basis of the findings from the SCOUT trial and the overall review of benefit/risk, Abbott proposes to implement risk management activities to ensure appropriate use of Meridia. These activities include further refinement of the USPI and specific prescriber and patient tools to encourage appropriate patient selection and use. These are further described in the following sections.

1.0 Proposed Label Changes

Abbott is proposing several changes to the Meridia USPI currently in use (implemented in January 2010). These proposed changes include:

- Addition of a Boxed Warning, to reinforce the contraindication for patients with a history of cardiovascular disease, and to adequately inform prescribers and patients about the importance of monitoring blood pressure, pulse and weight loss during treatment with Meridia.
- Addition of a description of the key SCOUT findings to the CLINICAL STUDIES section.
- Revisions to the INDICATIONS AND USAGE section to reinforce that Meridia is second-line therapy, to be used in patients who have not adequately responded to an appropriate diet and exercise weight-reducing program.
- Revisions to the DOSAGE AND ADMINISTRATION section to reinforce that treatment with Meridia should be discontinued in patients who do not respond adequately, for example, those patients who do not lose 4 pounds in the first 2 months of treatment, or whose weight loss stabilizes at less than 5% of their initial body weight within 3 months of starting therapy.
- Revisions to the WARNINGS section to provide more specific direction for monitoring blood pressure and pulse.

2.0 REMS

A REMS, consisting of a Medication Guide and the required Timetable for Assessments was approved by the Agency for Meridia on 04 August 2010. The focus of the

Medication Guide is to communicate the known risks of Meridia therapy, with a specific focus on the potential cardiovascular risks in patients with a history of cardiovascular disease. In addition to the approved Medication Guide, Abbott proposes to implement a Communication Plan for Meridia, including specific monitoring and education tools, to further educate and inform prescribers and patients of the appropriate use of Meridia.

2.1 Additional Proposed REMS Elements

2.1.1 Communication Plan

Abbott proposes to implement other communication and education tools as part of a risk management plan, to encourage appropriate use of Meridia. Examples of the key proposed tools, which are provided as Attachments 1 through 3, include:

- Attachment 1 - A Patient Screening Form for physician use, to assist prescribers in determining patient appropriateness.
- Attachment 2 - A Patient Monitoring Tool, to provide physicians with guidance on monitoring activities required during Meridia treatment.
- Attachment 3 - A Meridia Use and Monitoring Algorithm, as a 1-page reminder to physicians of appropriate patient selection and monitoring.

Abbott is also proposing to implement voluntary physician training, using a Web-based interface, to further communicate the potential risks and appropriate use of Meridia. The target audience for this training Web site will be any physician who prescribes Meridia (including both primary care physicians, as well as specialists).

The proposed Web site will include a link to the approved US package insert, the Medication Guide, and a summary of the key findings from SCOUT, and will ask physicians to register for follow-up contact from Abbott to evaluate awareness of the appropriate use of Meridia

At the time of implementation of the communication plan, Abbott proposes to distribute a Dear Health Care Professional letter, to advise physicians of the approved program and labeling changes.

2.1.2 Evaluation of REMS Elements

Following approval by the Agency of the proposed medications described above, evaluation of effectiveness of the proposed tools will be included with the required assessments for a REMS, to be performed at 18 months, 3 years, and 7 years after approval of the REMS program.

The proposed assessments will include:

- Quantitative market research conducted with a random sample of key physician prescribers across the US who have registered on the educational Web site, in order to assess the awareness, reach, recall, and overall effectiveness of Meridia educational materials. The quantitative market research will strive to understand overall awareness and recall of risks of Meridia therapy including overall knowledge of Meridia cardiovascular-related risks. Information from the quantitative market research will be used to refine and improve appropriate use messaging and communication vehicles, and to assess the overall impact of the Meridia communication tools.
- A patient understanding survey will be conducted to assess patient understanding of the key information contained in the Medication Guide.

MERIDIA® (sibutramine hydrochloride monohydrate)
Patient Screening Form

Name of patient	Age	Date

NOTE: MERIDIA **MUST NOT** be used by patients who have any of the following:

Please mark accordingly	YES	NO
● Does patient have, or a history of, any of the following? - coronary artery disease (e.g., angina, myocardial infarction) - congestive heart failure - tachycardia - peripheral arterial occlusive disease - arrhythmia - cerebrovascular disease (stroke or transient ischemic attack)		
● Does patient have inadequately controlled hypertension (>145/90 mmHg)?		
● Is patient older than 65 years of age?		
● Is patient younger than 16 years of age?		
● Does patient have any known hypersensitivity to sibutramine or any other component of the product?		
● Is patient currently taking/has been taking monoamine oxidase inhibitors (MAOIs) during the past 2 weeks?		
● Is patient currently taking/has been taking other centrally acting drugs for weight reduction?		
● Does patient have a major eating disorder such as anorexia nervosa or bulimia nervosa?		
● Does patient have a Body Mass Index $\leq$30 kg/m^2 or $\leq$27 kg/m^2 in the presence of other co-morbidities (dyslipidemia, diabetes)?		
REMINDER: If response was YES to any of the above, then the patient MUST NOT use sibutramine. Please refer to MERIDIA USPI for additional information.		

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MERIDIA® (sibutramine hydrochloride monohydrate)
Patient Monitoring Form*

Time	Monitoring pulse and blood pressure	Discontinue use if:
Months 1 and 2	Every 2 weeks	• At 2 consecutive visits, increase in pulse ≥10 bpm or systolic/diastolic blood pressure ≥10 mmHg, or blood pressure exceeds 145/90 mmHg • Patient has not lost 2 kg (4.2 lbs) on 15 mg dose
Month 3	Every 2 weeks	• At 2 consecutive visits, increase in pulse ≥10 bpm or systolic/diastolic blood pressure ≥10 mmHg, or blood pressure exceeds 145/90 mmHg • Weight loss <5% of initial body weight after 3 months of treatment
Months 4–6	Every month	• At 2 consecutive visits, increase in pulse ≥10 bpm or systolic/diastolic blood pressure ≥10 mmHg, or blood pressure exceeds 145/90 mmHg • Weight regain of >3 kg (6.6 lbs) from previously achieved weight loss
Months 7–24	At least every 3 months	• At 2 consecutive visits, increase in pulse ≥10 bpm or systolic/diastolic blood pressure ≥10 mmHg, or blood pressure exceeds 145/90 mmHg • Weight regain of >3 kg (6.6 lbs) from previously achieved weight loss • Treatment duration not to exceed 24 months

*** Please refer to USPI for additional information.**

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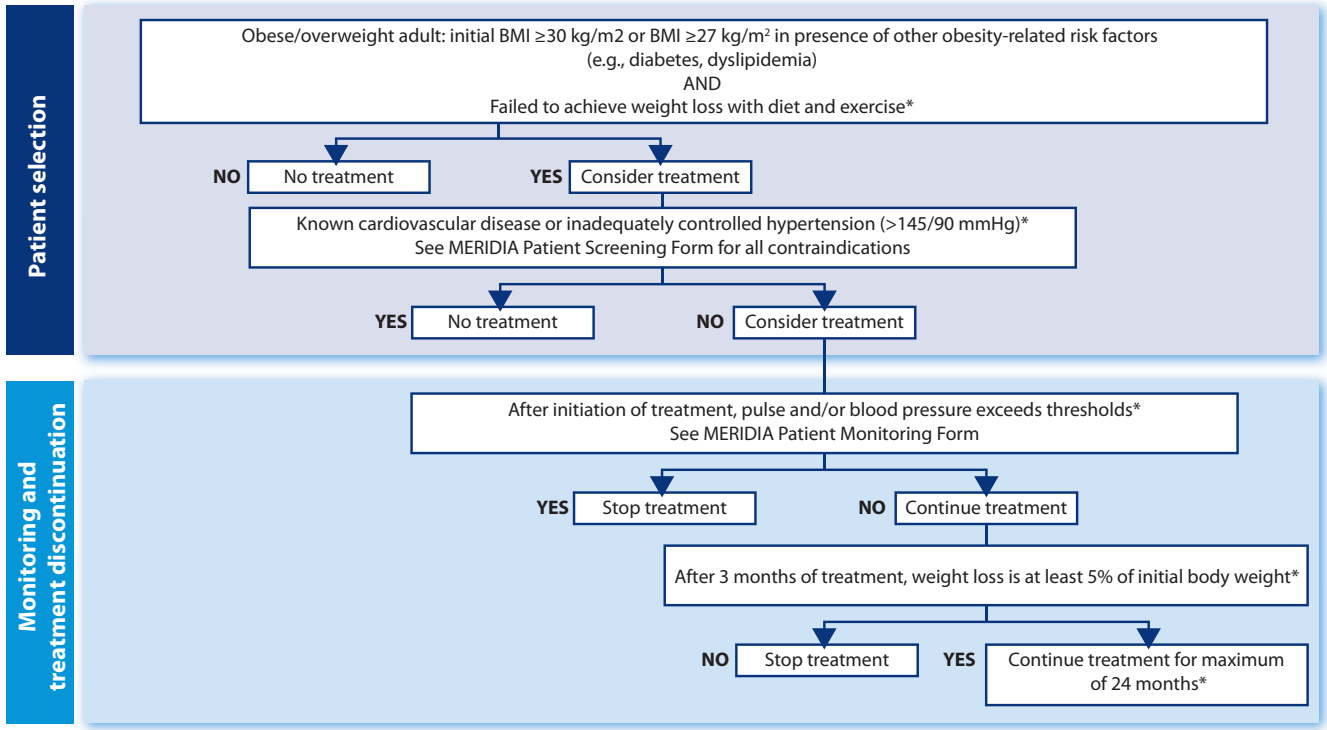
MERIDIA® (sibutramine hydrochloride monohydrate) Use and Monitoring Algorithm



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* See USPI